CITY OF HOPE NATIONAL MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF MEDICAL ONCOLOGY AND MOLECULAR THERAPEUTICS

TITLE: Phase II Study of Neratinib in Patients 60 and Older with HER2 Positive Metastatic Breast Cancer

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 15342 PROTOCOL DATE: 04/30/2019

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SITE: Breast
STAGE (If applicable): IV
MODALITY: Chemotherapy
TYPE: Phase II

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DEPARTMENT OF MEDICAL ONCOLOGY AND MOLECULAR THERAPEUTICS

PHASE II STUDY OF NERATINIB IN PATIENTS 60 AND OLDER WITH HER2 POSITIVE METASTATIC BREAST CANCER

IRB PROTOCOL NUMBER: 15342	**VERSION**: 23
DISEASE SITE:	Breast
STAGE:	III-IV
MODALITY	Oral
PHASE	Phase II
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STUDY SPONSOR AND MONITOR:	City of Hope National Cancer Center
AGENT NSC# AND IND#:	Neratinib, 066783

COORDINATING CENTER:

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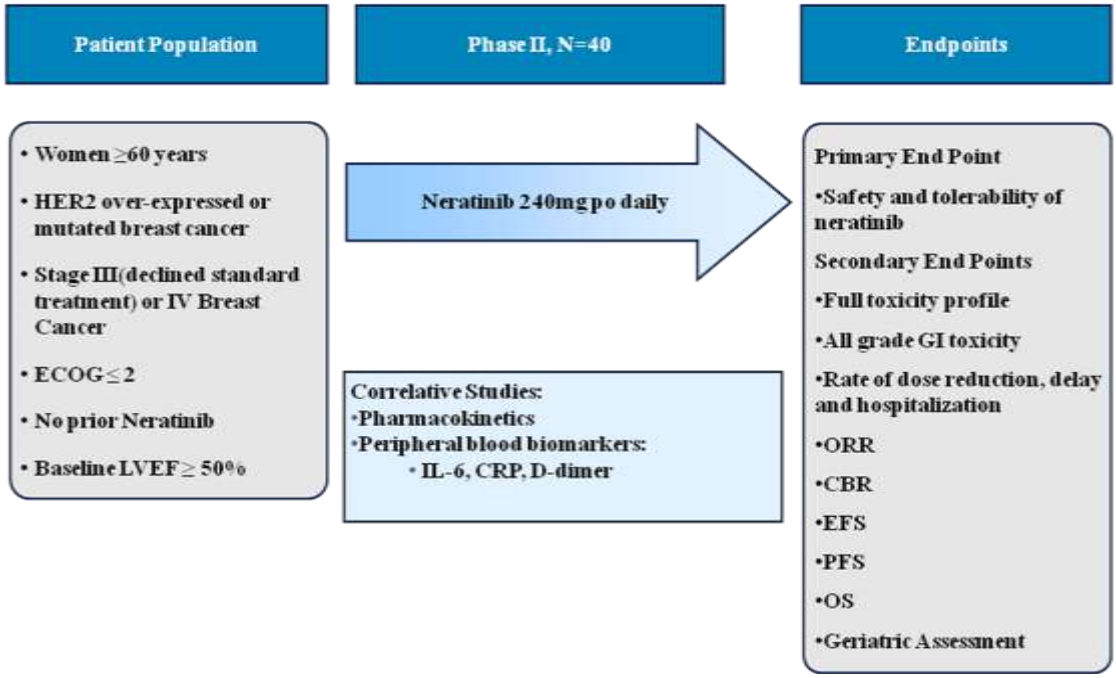
Experimental Design Schema

	Pre-Study (up to 28 days prior to enrolling)[i]	Cycle 1 Day 1 (28 day cycle)	Cycle 1 Day 8 (± 1 day)	Cycle 1 Day 15 (± 1 day)	Cycle 2 Day 1 (± 3 days)	Cycle 2 Day 15 (± 3 days)	Cycle 3 Day 1 (± 3 days)	Cycle 4 Day 1 (± 3 days)	Cycle 5 Day 1 (±3 days)	Cycle 6 Day 1 (±3 days)	Every Cycle Thereafter (± 3 days)	Every 3 cycles (±7 days)	Off treatment[h]
Neratinib (day 1-28 every 4 weeks [a,b]		X	X	X	X	X	X	X	X	X	X		
Demographics	X												
Medical history	X												
Concurrent meds (± 1 wk)	X	X			X		X	X	X	X	X		X
Physical exam (± 1 wk)	X	X			X		X	X	X	X	X		X
Vital signs (± 1 wk)	X	X			X		X	X	X	X	X		X
Height	X												
Weight (± 1 wk)	X	X	X	X	X	X	X	X	X	X	X		X
Performance Status (± 1 wk)	X	X			X		X	X	X	X	X		X
CBC w/diff, plts (± 1 wk)	X	X			X		X	X	X	X	X		X
Complete Metabolic Panel[c] (± 1 wk)	X	X	X	X	X	X	X	X	X	X	X		X
Diarrhea Checklist		X[l]											
Nurse brief toxicity evaluation		X	X	X	X	X	X						
EKG	X												
Pharmacokinetic samples [j]				X			X	X					
Adherence evaluation (pill count, diaries) (± 1 wk)		X	X	X	X	X	X	X	X	X	X		
Adverse event evaluation (± 1wk)		X	X	X	X	X	X	X	X	X	X		X
Tumor measurements using CT or PET-CT (± 1 wk)	X[d]							X				X[e]	X[f]
LVEF Assessment	X[d]							X[e]				X[e]	X[f]

Geriatric Assessment Survey(±1 wk) [k]	X							X					X[g]
Peripheral Blood Correlatives[k]	X							X					X
Bacteriomic profiling	X[m]			X	X	X	X						

a: Dose as assigned; neratinib 240mg orally daily; Doses held due to toxicity will not be made up.
b: If baseline laboratory tests are done within 14 days of start of treatment, these labs do not need to be repeated prior to Day 1.
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
d: Baseline assessment may be done up to 30 days prior to study enrollment.
e: Tumor measurements and LVEF assessment are repeated every 3 cycles ± 1 wk until patient comes off study. Documentation (radiologic or clinical) must be provided for patients removed from study for progressive disease.
f: Off-study radiologic evaluation will only be done if clinically indicated.
g: Geriatric assessment will be performed at baseline prior to study, after 3 cycles and at end of study. Geriatric assessment will be repeated off study ONLY if it had not been administered within the previous month. If patient's native language was not covered by the current language forms, Geriatric assessment form can be omitted with clear documentation.
h: Patients will be followed for 30 days following discontinuation of therapy in order to capture toxicity attributable to therapy.
i. Chart review data must be within 28 days to determine if patient meets study criteria. Once patient meets study criteria, then all criteria must be within window specified in protocol from Day 1 as indicated in column one in the schema above.
j: Pharmacokinetics samples will be collected at the following time points: Cycle 1 Day 15 pre-dose (± 20 minutes) and 6 hours post-dose (± 60 minutes); pre-dose (± 20 minutes) on Cycle 3 Day 1 and Cycle 4 Day 1.All pre-dose samples should be collected within 30 minutes before the daily dose, in 10 ml purple-top tube.
k: Peripheral blood correlatives for inflammatory marker measurement (IL-6, CRP and D-dimer) and ctDNA will be collected at baseline, after 3 cycles (Cycle 4 Day 1,±7days), and at end of study (±7days) when patient receives geriatric assessment in 10 ml purple-top tube.
L: An "Optimal Management of Diarrhea Checklist" will be reviewed and signed by study investigator or study nurse on Cycle 1 Day1. The study team will call patients at 1day, 2 days and 3 days after first dose of neratinib to assess tolerance.
m. Stool samples must be collected within 7 days prior to start of neratinib, at onset of first episode of diarrhea (same day), C1Day 15 (+/-3 days), C2Day1 (+/-3 days), C2Day15 (+/-3 days), C3Day1 (+/-3 days).

Study Schema



Protocol Synopsis

Protocol Title:
PHASE II STUDY OF NERATINIB IN PATIENTS 60 AND OLDER WITH HER2 POSITIVE METASTATIC BREAST CANCER
Brief Protocol Title for the Lay Public (if applicable):
Neratinib in Older Adults
Study Phase:
Phase II
Participating Sites:
City of Hope Comprehensive Cancer Center
Rationale for this Study:
Limited evidence exists to guide therapy with targeted agents in the older adult because these patients have been under-represented in clinical trials. Adults age 70 and older make up only 20% of subjects enrolled in FDA registration trials, but 46% of all patients with cancer are older adults. Dose-finding studies specifically in older adults are not routinely performed despite changes in drug metabolism, absorption, and distribution with increasing age. Neratinib is a potent oral small molecule that inhibits HER1, HER2 and HER4 at the intracellular tyrosine kinase domains through irreversible binding at a targeted cysteine residue in the ATP binding pocket of the receptor. Both the ability of neratinib to concurrently block signal transduction through the three active tyrosine kinase HER receptors, and its irreversible binding and prolonged inhibition of these growth-promoting pathways, provide the opportunity to further improve the clinical benefit of its use in HER2+ MBC patients. Early clinical data have demonstrated the activity of neratinib in patients who have already progressed through treatment with other small molecule or antibody-based HER2 targeted therapies. With the promising results from multiple clinical trials, neratinib has the potential to emerge as a novel therapy for patients with HER2 positive breast cancer. There is significant interest in studying this drug among older adults, as it is a targeted therapy which is convenient to prescribe and easy to administer. However, there is a significant amount of GI toxicity. In particular, grades 1-4 diarrhea occurred in 92% of patients. Grade 3-4 diarrhea occurred in over 30% of patients and dose reductions secondary to diarrhea range from 20-53% across 9 trials of neratinib alone or in combination with other therapy [1-9]. This particular side effect is likely to be significant in the population of older adults who are particularly vulnerable to diarrhea. Currently, there are 6 trials of neratinib therapy with a total enrollment of 291 patients, but only 38 patients are 65 and older (data provided by PUMA). Therefore, there is a significant gap of knowledge regarding the toxicity profile of neratinib in older adults, as well as the optimal supportive care medications to minimize side effects.

Objectives:

Primary Objective:

To estimate the rate of grade 2 or higher toxicities attributed to neratinib in adults 60 years and older with HER2 overexpressing breast cancer.

Secondary Objectives:

- To describe the full toxicity profile including all grades as measured by NCI CTCAE v.4.0.
- To estimate the rate of all grades of GI toxicities such as diarrhea, nausea, and vomiting.
- To estimate the rate of dose reduction, holds and hospitalizations.
- To describe pharmacokinetic parameters of neratinib in adults 60 and older.
- To estimate overall response rate (ORR) and clinical benefit rate (CBR) defined by RECIST 1.1.
- To estimate event free survival (EFS), progression free survival (PFS) and overall survival (OS).
- To evaluate the role of cancer-specific geriatric assessment tool in predicting treatment toxicities.
- To estimate adherence rate to neratinib in older adults.
- To explore the association of PK parameters and geriatric assessment findings.
- To explore if serum biomarkers of aging (IL-6, CRP, and D-dimer) are associated with treatment toxicities.

Endpoints:

Primary: Grade 2 or higher toxicities.

Secondary:

- All grade toxicities as measured by NCI CTCAE v.4.0.
- All grades of GI toxicities such as diarrhea, nausea, and vomiting.
- Dose reduction, holds and hospitalizations.
- Effect of age on PK parameters: clearance and volume of distribution and exposure-response relationships on efficacy and safety of neratinib.
- Response as defined by RECIST.
- EFS(where the event is toxicity or progression), PFS, OS.
- Geriatric assessment score
- Adherence as defined by pill count.
- IL-6
- CRP
- D-dimer

Study Design:

The study will be an open label, single arm, phase II toxicity study of single agent neratinib in order to describe the toxicity profile in patients age 60 and older with HER2 positive

breast cancer. We plan to study 40 subjects, stratified by patient age (with at least 5 patients age 75 years or older, and no more than 15 patients 60-70, in order to assure that we study the entire age range of older adults). As diarrhea has been seen with neratinib, we have established additional guidelines and criteria which will be used to flag an unexpected number of patients that experience grade 3 diarrhea within the 2 cycles on neratinib treatment in the presence of aggressive mandatory anti-diarrhea management which will lead to a careful data review. There will also be one interim analysis of the toxicity profile after 20 subjects have been on drug for at least one cycle.

Patients are anticipated to participate in the study for an average of 48 months. This includes approximately 0.5 months for screening, an estimated average of 9.5 months for the active treatment phase, and an estimated average of 38 months for the long-term follow-up phase. Treatment is to be given for as long as it is tolerated and while there is no disease progression. Patients who permanently discontinue treatment will enter the long-term follow-up phase until death or withdrawal of consent.

Sample Size:

40

Estimated Duration of the Study

48 months

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

1. Female or male patient age ≥ 60 years.
2. ECOG performance 0-2. (see Appendix A for ECOG criteria)
3. Life expectancy of greater than 12 weeks.
4. Histologically or cytologically proven metastatic breast cancer (metastases can be proven with imaging results in certain circumstances provided that the initial tumor was demonstrated histologically).
5. Stage IV Her2/Neu positive breast cancer patients who failed previous anti-HER2 targeted therapies.
6. HER2 positivity as defined by ASCO/CAP guidelines.

If HER2 negative by IHC or FISH, but activating somatic mutations of HER2 gene identified through genomic sequencing (CLIA certified lab test) including but not limited to the following: Missense substitutions (G309A, G309E, S310F, S310Y, S653C, V659E, R678Q, V697L, T733I, L755S, L755P, D769H, D769Y, D769N, G776V, G776C, V777L, L841V, V842I, R849W, L869R); Insertions/deletions (A775_G776insYVMA aka Y772_A755dup, G776VinsC, G776AinsVGC, G778_S779insCPG, P780_781insGSP aka G778_P780dup, L755_T759del) and/or HER3 activating mutations.

1. There is no limitation on the number of prior lines of systemic therapy or HER2-targeted therapies (prior neratinib not allowed).
2. Both measurable as well as non-measurable disease will be allowed.
3. Adequate organ and bone marrow functions defined below within 4 weeks of pre-

registration:
    - Hemoglobin: ≥9 g/dL (after transfusion, if necessary).
    - Total bilirubin: within normal institutional limits.
    - AST (SGOT)/ALT (SGPT): ≤ 2.5 X institutional upper limit of normal.
    - Creatinine clearance ≥ 30 mL/min as calculated by Cockroft-Gault formula.
4. Baseline left ventricular ejection fraction LVEF ≥ 50% as evaluated by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA).
5. All grade ≥2 toxicities other than alopecia from prior therapy have resolved by the time of study commencement.
6. Patient must have completed radiation therapy with adequate recovery of bone marrow and organ functions, before starting neratinib.
7. Patient with stable or treated brain metastases are eligible. Asymptomatic patients with metastatic brain disease who have been on a stable dose of corticosteroids for treatment of brain metastases for at least 14 days are eligible to participate in the study.
8. Provide written, informed consent to participate in the study and follow the study procedures.

Exclusion Criteria:

1. Prior treatment with neratinib.
2. Concurrent usage of other investigational agents, chemotherapy, or hormone therapy. Prior chemotherapy, hormonal therapy, targeted therapy, and investigational agents are allowed but all toxicities grade ≥2 must have resolved by the time of study commencement (except alopecia).
3. Any major surgery ≤ 28 days prior to the initiation of investigational products.
4. Received chemotherapy or biologic therapy ≤3 weeks prior to the start of neratinib
5. Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2, including individuals who currently use digitalis specifically for congestive heart failure), unstable angina, myocardial infarction within 12 month of enrollment or ventricular arrhythmia.
6. Concurrent use of digoxin due to cardiac disease. QTc interval ≥ 450 milliseconds in men or QTc interval ≥ 470 milliseconds in women within 2 weeks of registration or known history of QTc prolongation or Torsades de Pointes.
7. Inability to take oral medication.
8. Other malignancy within the past 3 years with the exception of: a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) cervix or vulva carcinoma in situ; c) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder, or benign tumors of the adrenal or pancreas.
9. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (e.g., Crohn's disease, malabsorption, or Grade ≥2 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE v.4.0] diarrhea of any etiology at baseline).
10. Known clinically active infection with hepatitis B or hepatitis C virus.

11. Evidence of significant medical illness, abnormal laboratory finding or psychiatric illness/social situations that would, in the Investigator's judgment, makes the patient inappropriate for this study.

Investigational Product Dosage and Administration:

Neratinib will be given as 240 mg (six 40 mg tablets) orally, once daily with food, preferably in the morning, continuously throughout the study period, with no rest between cycles. This medication will be continued until disease progression, death, drug intolerance or other limiting factors, removal from protocol due to patient or physician preference, or loss to follow-up.

Clinical Observations and Tests to be Performed:

Patients who fulfill the eligibility criteria described above will undergo the full informed consent process. Prior to starting treatment, all subjects will undergo history and physical exam, and laboratories including CBC, chemistry, and liver function tests. Pathology will be reviewed and HER2 receptor status will be documented. HER 2 receptor somatic mutations will be documented if available. Baseline disease will be documented with CT scan of chest, abdomen and pelvis, or PET-CT as long as there is a diagnostic CT component (within 30 days prior to starting treatment). All subjects will have cardiac function evaluation (within 30 days prior to starting treatment) using either an echocardiogram or MUGA scan and an EKG.

Each cycle will be four weeks with neratinib 240 mg orally continued daily. During each cycle, history and physical, CBC and CMP (BMP, LFTs) will be performed once every 4 weeks (+/- 1 wk). Toxicity will be evaluated at these appointments as well between visits if the subject contacts the participating clinician with concerns. Evaluations will continue once per cycle until disease progression, death, discontinuation of the drug, or loss to follow-up.

Due to the risk of diarrhea in this population, research nurse will contact the patient on each day days 1-3 to check on diarrhea and loperamide compliance. During the first cycle (Cycle 1 Day 8 and Day 15) and part of the second cycle (Cycle 2 Day 15, the patient will be seen at a brief nurse visit during those weeks in which no full physician assessment is required. During these visits, adverse events, limited history and physical exams will be done to ensure that any severe side effects that could benefit from intervention are identified.

While on study, CT of the chest, abdomen, and pelvis (or PET-CT as above); and LVEF evaluation will be performed at the end of every three cycles (every 12 weeks). The modality of cardiac evaluation must be consistent throughout the study for each individual patient.

A cancer specific geriatric assessment will be performed at baseline, after 3 cycles, and at the end of the study. The comprehensive cancer-specific geriatric assessment includes an evaluation of functional status, co-morbidity, cognition, psychological status, social functioning and support, and nutritional status.[10] Patients receiving at least 1 dose of investigational product will be evaluable for safety. Safety will be assessed based on medical history, vital sign measurements, physical examination findings, ECG results, MUGA or ECHO and laboratory assessments. Adverse events (AEs) will be graded

according to the NCI CTCAE v.4.0. AEs and SAEs will be reported until 28 days after the last dose of investigational product and will be followed until resolution or until condition stabilizes. Should an investigator be made aware of any neratinib-related SAE occurring any time after the reporting period, it should be promptly reported.

Adherence to neratinib will be measured by pill count at each appointment as well as by patient self-report in dedicated patient diaries, also to be evaluated at each interim visit. Neratinib log will also be utilized to track the use of the pill. In the event of discrepancy in these measures of adherence, we will follow whichever indicates the lower measure of adherence (i.e. if patient states they took 13 of 14 doses, but only 10 doses are missing, we will count the patient as having taken only 10 days. Alternatively, if 14 doses are missing, but the patient stated she only took 11 doses, we will count the patient as having taken only 11 doses.) Measures of patient initiated dose reduction will be exclusively measured by patient self-report. All toxicity related dose interruptions or reductions, hospitalizations, and adverse events will be noted. Subjects will be followed for toxicity outcomes for an additional 30 days after stopping the drug and until resolution of all grade $\geq$2 toxicities.

Pharmacokinetic measures will be determined in all study participants. Based on a neratinib half-life of 11-20 hours at steady state, PK samples will be collected at the following time points: Cycle 1 Day 15 pre-dose (± 20 minutes), 6 hours post-dose ± 60 minutes) and Day 1 of Cycle 3 and 4 pre-dose (± 20minutes). All pre-dose samples should be collected within 30 minutes before the daily dose. In the event that the neratinib dose is held or the dose level is changed, pharmacokinetic sample will be rescheduled accordingly.

Mandatory Peripheral blood biomarkers (IL-6, CRP, and D-dimer) and proteomics analysis will be performed at baseline, after 3 cycles, and at the end of the study.

Statistical Considerations:

Tables will be created to summarize the toxicities and side effects by organ system, attribution and severity for all participants that receive at least one dose of neratinib. Rates and associated 95% exact Clopper and Pearson binomial confidence limits will be estimated for 1) grade 2 or higher toxicities attributed to neratinib, 2) all grade GI toxicities (diarrhea, nausea and vomiting), 3) dose reductions, holds and hospitalizations, and 4) the objective response (CR+PR) and clinical benefit (CR+PR+SD) and 5) 16 week progression free survival(PFS). EFS, PFS and OS will be estimated using the product limit method of Kaplan and Meier. Descriptive statistics will be provided for pharmacokinetic parameters, drug adherence and participant demographics. Generalized linear models and graphical methods will be used to explore factors as identified by a cancer-specific geriatric assessment and serum biomarkers that may be predictive of toxicity dose reductions, dose holds or hospitalizations. We will use generalized linear models to determine if any of these factors independently predict toxicity, response, and/or pharmacokinetic parameters of interest.

Sponsor/Licensee:

Puma Biotechnology Inc.

Case Report Forms

Paper or via Medi-data Electronic Data Collection (EDC)

Table of Contents

Background/ Study Rationale

1.1 Introduction/Rationale for Development

Approximately 15-20% of women with breast cancer have HER2+ cancer, which is associated with aggressive disease and poor prognosis. The goal of this study is to utilize a phase II design to examine the tolerability of neratinib, a potent oral small molecule tyrosine kinase inhibitor targeted at ERBB1, 2, and 4 among older adults with HER2 overexpressing breast tumors. There is significant interest in studying this drug among the older adults as it is an oral targeted therapy. However, there is concern that without definitive studies in the older adult population, oncologists may have reservations in giving neratinib, or will dose reduce the agent without guidance.

1.2 Overview of Proposed Study: Cancer and Aging

Cancer is a disease that disproportionately affects older patients. People age 65 and older have an 11-fold increase in the incidence of cancer and a 15-fold increase in cancer mortality in comparison to people younger than age 60 [11, 12]. Older adults are an important population to study because 60% of all cancer cases and 70% of cancer mortality occur in patients over the age of 60 [13]. The number of older people with cancer is continuously growing as the population is aging. By the year 2030, the total projected cancer incidence will increase by approximately 45%, from 1.6 million in 2010 to 2.3 million in 2030. A 67% increase in cancer incidence is anticipated for older adults, compared with an 11% increase for younger adults [14]. Older adults with cancer are an understudied population. Cancer patients age 70 or greater made up only 20% of subjects enrolled in FDA registration trials from 1995 to 1999, though they made up fully 46% of the U.S. cancer population [15].

While several studies have demonstrated that older adults are more likely to experience chemotherapy toxicity [16-18], the comparative risk of targeted therapies has been under-studied. Though chronological age does not entirely correlate with physiologic age, older adults do have changes in physiology that can predispose to drug toxicity [19]. A progressive reduction in the functional reserve of various organ systems may alter the pharmacokinetics of anti-cancer therapies[20] and increase the susceptibility of older individuals to complications of treatment[21, 22] Normal tissues may be less able to repair the molecular damage caused by antineoplastic agents due to cellular senescence, resulting in greater potential cardiac toxicity, neurotoxicity, mucositis, and hematologic toxicities [19]. And finally, there may be age-related changes in the biology of cancer which may impact the therapeutic efficacy and approach to treatment [23-26].

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

1.3 Epidermal Growth Factor Receptor (ErbB Receptors) Family

The human epidermal growth factor receptor 2 (HER2)/Neu gene is a member of the family of EGFR/ErbB genes. Amplification or over-expression is associated with an aggressive disease biology, including enhanced cell proliferation, and reduced progression-free survival (PFS) and overall survival (OS) [27] [28-30]. The human HER (ErbB) receptor family consists of four closely related transmembrane tyrosine kinase receptors: epidermal growth factor receptor ErbB1 (HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). These membrane-spanning

proteins receive extracellular signals from small peptide ligand molecules, including epidermal growth factor-like molecules, transforming growth factor-α and neuregulins. Ligand binding triggers intracellular signaling through a complex and tightly controlled array of signaling pathways that together drive and regulate many cellular functions, including cell proliferation, organ development, and repair. Binding of ligands to extracellular parts of HER1, HER3 and HER4 result in dimerization and initiation of a series of signaling cascades that include mitogen-activated protein kinase (MAPK), phosphoinositide-3kinase (PI3K), protein kinase B (PKB or Akt), and mammalian target of rapamycin (mTOR) [31].

HER receptor dimerization is an essential requirement for signaling activity and can occur between two different HER receptors (heterodimerization) or two molecules of the same receptor (homodimerization) [32, 33]. HER homodimers weakly perpetuate signals compared with heterodimers [34]. Ligands have been identified for the HER1 (EGFR), HER3 and HER4 receptors. No ligand has yet been identified for HER2 (also known as Her-2/Neu) which is the preferred dimerization partner for HER1, HER3, and HER4[34]. The HER2 receptor is presumed to exert its effects through formation of heterodimers with other HER family members. HER3 possesses a defective tyrosine kinase and requires heterodimerization with another HER member to be activated. HER4 has an active tyrosine kinase, but its role in breast cancer is currently unknown. HER1 (EGFR) and HER2 receptors are often upregulated in many human cancers [35]. Many therapeutic strategies have therefore been employed to block the HER signaling pathways as a means to improve the therapeutic efficacy of hormonal and chemotherapy regimens.

1.4 Human Studies – HER2 Targeted Therapies in Breast Cancer

1.4.1 Trastuzumab

Human epidermal growth factor receptor 2 (HER2) amplification is seen in approximately 15-20% of breast cancers and is associated with more aggressive disease and worse prognosis. Trastuzumab, the first agent approved for treatment of HER2+ breast cancer, is a monoclonal antibody against the extracellular juxtamembrane portion of the HER2 receptor. Treatment results in improved DFS and OS in patients with HER2-over-expressing tumors in both the adjuvant and metastatic settings [36]. In adjuvant trials, trastuzumab has been shown to decrease the risk of recurrence of breast cancer by 39-52% [37-39]and decreases the risk of death by 33% [38]. Trastuzumab has also been found effective in the neoadjuvant setting [16, 18].

The mechanisms of action of trastuzumab include prevention of HER2-receptor dimerization, increased endocytotic destruction of the receptor, inhibition of shedding the extra-cellular domain, and immune activation [40] by recruiting immune effector cells that are responsible for antibody-dependent cytotoxicity[41]. Trastuzumab was first approved for use in the treatment of HER2-amplified breast cancer in the U.S. in 1998. More recently, additional HER2-targeted therapies including lapatinib (a tyrosine kinase inhibitor), pertuzumab (a humanized anti-HER2 monoclonal antibody) and TDM-1 have shown promising results in metastatic HER2 positive breast cancer.

1.4.2 Pertuzumab

Pertuzumab is a monoclonal antibody that binds HER2 at a different epitope of the HER2 extracellular domain (subdomain II) than trastuzumab [42] and prevents HER2 from dimerizing

with other ligand-activated HER receptors, most notably HER3 [43, 44]. Adding pertuzumab to combination therapy has led to improved PFS in patients with HER2 metastatic breast cancer (MBC) and higher RR in pre-operative setting[45]. The clinical evaluation of pertuzumab and trastuzumab (CLEOPATRA) assessed the efficacy and safety of pertuzumab plus trastuzumab and docetaxel, as compared with placebo plus trastuzumab and docetaxel (control group), as first-line treatment for patients with HER2+ MBC who had not received chemotherapy or biologic therapy for their metastatic disease [42]. Based on an interim analysis (on 43% of the total number of events planned for the final analysis), treatment with pertuzumab plus trastuzumab and docetaxel compared with the control group resulted in a significant reduction in the risk of progression or death, and an increase of 6.1 months in median [42]. The median PFS in the control group (12.4 months) was similar to that among HER2+ MBC patients in two other randomized studies who were treated with the combination of trastuzumab and docetaxel (11.7 months[46] and 11.1 months[39]). CLEOPATRA findings suggest that targeting HER2+ tumors with two anti-HER2 monoclonal antibodies (dual HER2 targeting) that have complementary mechanisms of action results in a more comprehensive blockade of HER2. These findings highlight the clinical importance of preventing the ligand-dependent formation of HER2 dimers in order to silence HER2 signaling to the greatest extent possible [34, 43]. Pertuzumab received approval in the U.S. in 2012 for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2+ MBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

1.4.3 Ado-Trastuzumab Emtansine (T-DM1 [Kadcyla])

T-DM1is an antibody-drug conjugate that combines HER2-targeted delivery of the potent antimicrotubule agent emtansine (DM1, a derivative of the antimicrotubule agent maytansine), with the antitumor activity of trastuzumab [47, 48]. In T-DM1, trastuzumab and DM1 are covalently linked via a stable thioether linker (*N*-maleimidomethyl) cyclohexane-1-carboxylate, which is thought to limit the exposure of normal tissue to DM1[49]. Antitumor activity was established in a proof-of-concept Phase 2 study of single-agent T-DM1 in patients with HER2+ MBC, who had progressed while receiving HER2-directed therapy[50]. Furthermore, in a single-arm phase 2 study, T-DM1 demonstrated efficacy in patients with HER2+ MBC who previously received all standard HER2-directed therapies (trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine) [51].

1.4.4 Lapatinib

Another HER2-targeted agent is lapatinib, an oral, selective, reversible, small molecule that targets the tyrosine kinase domains of both HER1 and HER2 [52]. *In vitro* studies confirmed that lapatinib inhibits growth [52] and can lead to cell arrest or apoptosis[53] in human tumor cells overexpressing HER1 or HER2. Furthermore, lapatinib treatment has been shown to inhibit the growth of HER2-overexpressing human breast cancer cells that do not respond to trastuzumab after long-term conditioning[54]. Investigations of lapatinib monotherapy conducted in highly refractory MBC patients showed modest cytoreduction and disease stabilization in a trastuzumab-refractory setting [55]. A randomized phase III clinical trial including women with HER2-overexpressing advanced breast cancer who had progressed on a regimen containing trastuzumab, showed that lapatinib in combination with capecitabine was superior to capecitabine alone[19] This study ultimately resulted in FDA approval for lapatinib in 2007 in

combination with capecitabine. Additionally, a Phase III trial showing that lapatinib in combination with letrozole, an aromatase inhibitor, was effective in the first-line metastatic setting in a subset of 219 patients whose breast cancer was HER-2 positive and hormone receptor positive. Median progression-free survival was 8.2 months for those receiving letrozole and lapatinib versus 3.0 months for those getting letrozole alone (HR 0.71 [0.53-0.96], p=0.019) [27].

Currently there is an on-going designated study accessing the tolerance and efficacy of lapatinib plus trastuzumab in patients who are 60 and older with locally advanced or metastatic HER2 overexpressing breast cancer (NCT01273610).

1.4.5 Neratinib in HER2 Positive Breast Cancer

Neratinib (PB-272, HKI-272) is a potent irreversible pan–erythroblastic leukemia viral oncogene homolog (ERBB) tyrosine kinase inhibitor (TKI) that blocks signal transduction through 3 epidermal growth factor receptors (EGFRs): EGFR (encoded by *ERBB1)*, HER2 (encoded by *ERBB2)* also known as human epidermal growth factor receptor 2, and HER4 (encoded by *ERBB4*), or their active heterodimers with HER3 (encoded by *ERBB3*). Treatment with neratinib results in sustained inhibition of these growth-promoting pathways in subjects with HER2-positive or HER2-mutant breast and other cancers due to activating mutations in these *ERBB* genes. The ability of neratinib to concurrently block signal transduction through the three active tyrosine kinase HER receptors, and prolong inhibition of these growth-promoting pathways provides the opportunity to further improve the clinical benefit of its use in HER+ MBC patients.

1.4.5.1 Preclinical Data

Preclinical data suggest that neratinib has antitumor activity in HER1 and/or HER2-expressing carcinoma cell lines, with cellular IC50 <100 nM[18]. Neratinib may have advantages over other HER2 inhibitors, due to its ability to inhibit both HER1 and HER2, and to inhibit irreversibly. Breast cancer cells may become resistant to trastuzumab on the basis of ECD truncated HER2 receptor, which can no longer be recognized by the antibody[56], or because of co-activation of HER1 signaling [57]. However, since neratinib acts on the intracellular tyrosine kinase domain, such cells are likely to maintain sensitivity to neratinib [16]. *In vivo*, neratinib is active in HER2 and HER1-dependent tumor xenograft models, when administered orally on a once daily schedule. Overall, neratinib is less potent against HER1-dependent tumors than HER2-dependent tumors *in vivo*, although it has equivalent activity against the two kinases *in vitro*. The ability of neratinib to specifically inhibit HER1, HER2, and HER4 is unique among the small molecule TKIs and contrasts with the effects of the licensed TKIs gefitinib and erlotinib, which target EGFR only, and lapatinib, which reversibly targets HER1 and HER2[17]. Additional clinical benefit may be derived from agents such as neratinib that concurrently inhibit 3 HER receptors.

1.4.5.2 Neratinib Pharmacokinetic Data

Clinical pharmacokinetic (PK) results from the first-in-human study in healthy volunteers and subjects with cancer showed that the exposure of neratinib increased in a dose-dependent manner after oral administration of neratinib, and no accumulation of neratinib after daily dosing was observed when comparing Day 14 exposure with Day 1 exposure. Neratinib is absorbed within 4 to 6 hours. The half-life of neratinib, approximately 14 hours, supports a once-daily dose regimen. Fecal excretion of radiolabeled neratinib accounted for approximately 97% of the total

dose administered, and is the major route of elimination. Data suggested no sex-related effect on the PK profile of neratinib. Food appeared to increase neratinib Cmax and area under the plasma concentration-versus-time curve (AUC) by approximately 2-fold as shown in a food-effect assessment of a single ascending dose study with healthy subjects. A study in healthy volunteers suggests that severely hepatically-impaired (Child-Pugh C) subjects had statistically significant increased exposure and decreased elimination of neratinib. Results of a study with healthy subjects to assess the effects of neratinib on cardiac conduction showed that neratinib was not associated with prolongation of the QTc interval in humans at the recommended dose of neratinib 240 mg daily with food, or under conditions of supratherapeutic plasma concentrations, obtained by the concomitant administration of neratinib 240 mg and ketoconazole 400 mg.

Neratinib interactions with drugs that affect CYP3A4 and Flavin-containing monooxygenases (FMO) were not tested, since the metabolites of neratinib are formed by them *in vitro*. Systemic exposure to digoxin increased by 54% for Cmax and 32% for AUC when a single oral dose of digoxin 0.5 mg was coadministered with multiple oral doses of neratinib 240 mg compared with systemic exposure when digoxin was administered alone. No drug-drug interactions were observed when neratinib was concomitantly administered with paclitaxel or vinorelbine.

1.4.5.3 Overall Safety Profile – Safety Data of Pooled Single-Agent Studies

Single-agent unblinded safety data is available for 476 patients treated with neratinib (Neratinib Investigator brochure). Overall, 476 subjects with advanced solid tumors received neratinib monotherapy at dosages of 240 mg/day in 7 studies. All AEs (all grades and Grades ≥3), by system organ class and preferred term, occurring in at least 10% of subjects with advanced solid malignancies who received neratinib monotherapy at 240 mg (N=476) are presented in **Table 1**. The most commonly reported AE of any toxicity grade was diarrhea (88.2%) followed by nausea (46.2%), vomiting (35.5%), fatigue (33.6%), and decreased appetite (30.3%). The most commonly reported Grade 3 AE was diarrhea (27.1%).

1.4.5.4 Adverse Events Leading to Treatment Discontinuation

For subjects with cancer, diarrhea was the most frequently reported AE that led to the discontinuation of neratinib treatment. Pooled data on the incidences of AEs that led to discontinuation of subjects with advanced solid malignancies in 12 ongoing studies (N=4242 combined safety population) are summarized in **Table 2**. The most common AE that led to discontinuation was diarrhea (6.1%), followed by vomiting (1.5%) and nausea (1.2%). Grade 3 AEs that led to discontinuation were reported for 5.8% of the subjects, and Grade 4 AEs were reported for 0.5% of the subjects. The most frequent Grade 3 AEs that led to discontinuation were diarrhea (2.8%), vomiting (0.6%), ALT increased (0.3%), and fatigue (0.2%).

1.4.5.5 Diarrhea Prophylaxis in Neratinib Clinical Studies

Although in earlier Neratinib trials, patients received standard-of-care diarrhea management on occurrence of diarrhea, the studies did not mandate concomitant treatment with loperamide or other anti-diarrheal agents at the outset of neratinib therapy for prevention of neratinib-related diarrhea. In these studies, 28-39% of patients experienced Grade 3 or Grade 4 diarrhea (**Table 3**). In ongoing neratinib clinical studies that are currently enrolling patients with solid tumors, prophylactic use of antidiarrheal medication is mandatory, as shown in **Table 3**. Among patients

receiving prophylactic antidiarrheal medication in these studies, 12-16% of patients experienced Grade 3 or Grade 4 diarrhea.

Table 1: Summary of Adverse Events Reported in ≥10% of Subjects With Advanced Solid Malignancies Receiving Single-Agent Neratinib (240 mg, All Subjects). Maximum CTCAE Grade by Descending Frequency (Safety Population, Pooled Studies) *

Adverse Events	Number of Subjects (N=476)		
	Grade 1 to 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Any Adverse Event	**464 (97.5)**	**205 (43.1)**	**46 (9.7)**
Gastrointestinal Disorders	**440 (92.4)**	**145 (30.5)**	**4 (0.8)**
Diarrhea	420 (88.2)	129 (27.1) 14	3 (0.6)
Nausea	220 (46.2)	(2.9)	1 (0.2)
Vomiting	169 (35.5)	18 (3.8)	1 (0.2)
Abdominal Pain	104 (21.8)	7 (1.5)	0
General Disorders And Administration Site Conditions	**287 (60.3)**	**29 (6.1)**	**9 (1.9)**
Fatigue	160 (33.6)	14 (2.9)	0
Asthenia	68 (14.3)	9 (1.9)	1 (0.2)
Pyrexia	53 (11.1)	1 (0.2)	0
Metabolism And Nutrition Disorders	**214 (45.0)**	**43 (9.0)**	**4 (0.8)**
Decreased Appetite	144 (30.3)	17 (3.6)	0
Dehydration	52 (10.9)	17 (3.6)	1 (0.2)
Skin And Subcutaneous Tissue Disorders	**208 (43.7)**	**4 (0.8)**	**0**
Rash	83 (17.4)	0	0
Respiratory, Thoracic And Mediastinal Disorders	**193 (40.5)**	**29 (6.1)**	**13 (2.7)**
Dyspnea	80 (16.8)	20 (4.2)	9 (1.9)
Cough	70 (14.7)	3 (0.6)	0
Musculoskeletal And Connective Tissue Disorders	**173 (36.3)**	**18 (3.8)**	**1 (0.2)**
Back Pain	53 (11.1)	9 (1.9)	0
Investigations	**171 (35.9)**	**31 (6.5)**	**2 (0.4)**
Weight Decreased	54 (11.3)	0	0
Nervous System Disorders	**163 (34.2)**	**12 (2.5)**	**8 (1.7)**
Headache	85 (17.9)	5 (1.1)	0
Blood And Lymphatic System Disorders	**91 (19.1)**	**13 (2.7)**	**3 (0.6)**
Anemia	52 (10.9)	5 (1.1)	1 (0.2)

*Data provided by Puma Biotechnology Inc. (Investigator's Brochure)

Table 2: Incidence of Adverse Events Leading to Discontinuation Reported in ≥0.1% of Subjects With Advanced Solid Malignancies by System Organ Class and Preferred Term. Maximum CTCAE Grades, Descending Frequency (Safety Subjects, Pooled Studies)*

Adverse Events	Number of Subjects (N=4242)		
	Grade 1 to 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Metabolism And Nutrition Disorders	**16 (0.4)**	**5 (0.1)**	**0**
Decreased Appetite	9 (0.2)	1 (0.0)	0
Dehydration	4 (0.1)	2 (0.0)	0
Musculoskeletal And Connective Tissue Disorders	**16 (0.4)**	**4 (0.1)**	**0**
Arthralgia	3 (0.1)	0	0
Muscular Weakness	3 (0.1)	1 (0.0)	0
Pain In Extremity	3 (0.1)	1 (0.0)	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**14 (0.3)**	**6 (0.1)**	**3 (0.1)**
Metastases To Central Nervous System	3 (0.1)	1 (0.0)	0
Psychiatric Disorders	**12 (0.3)**	**2 (0.0)**	**0**
Anxiety	4 (0.1)	1 (0.0)	0
Depression	3 (0.1)	1 (0.0)	0
Renal And Urinary Disorders	**10 (0.2)**	**7 (0.2)**	**0**
Renal Failure	5 (0.1)	4 (0.1)	0
Vascular Disorders	**8 (0.2)**	**2 (0.0)**	**0**
Hypertension	3 (0.1	1 (0.0)	0

*Data provided by Puma Biotechnology Inc. (Investigator's Brochure)

Table 3: Diarrhea incidence in neratinib studies without loperamide prophylaxis *

Studies	Patients	Investigational Product	Patients N	Grade 3-4 Diarrhea n(%)
3144A1-201-WW	Locally advanced or HER2+ MBC	neratinib 240 mg	66	21 (32%)
3144A2-3003-WW	Locally advanced or HER2+ MBC	neratinib 240 mg (monotherapy arm)	116	33 (28%)
10-005	Triple-negative or HER2+ MBC	neratinib (240 mg) + temsirolimus IV (once per week)	35	10 (29%)
I-SPY2	HER2+/HR-Breast Cancer	neratinib (240 mg) + paclitaxel (once per week)	116	45 (39%)

*Data provided by Puma Biotechnology Inc. (Investigator's Brochure)

1.4.6 Clinical Trials of Neratinib

Neratinib is currently being developed for treatment of HER2-overexpressed or amplified breast cancer as well as HER2-mutant breast, non-small cell lung cancer (NSCLC), and other solid tumors. Additionally, clinical activity is being evaluated in *EGFR* mutation-positive and *ERBB3* mutation-positive solid tumors. Thirteen clinical studies are currently ongoing with neratinib both administered as monotherapy and in combination with other marketed drugs. Clinical

experience with orally administered neratinib is based on information obtained from 31 studies conducted with healthy subjects and in subjects with advanced solid tumors, including breast cancer and NSCLC. As of 22-AUG-2014, 5089 subjects have been enrolled in neratinib studies. Among the subjects enrolled, 476 subjects with locally advanced or metastatic solid malignancies have received at least 1 dose of single-agent neratinib at 240 mg administered once a day (QD), and approximately 1400 subjects have been dosed with neratinib 240 mg in the ongoing study, a randomized, double-blind, placebo-controlled (1:1 ratio) Phase 3 study of neratinib after trastuzumab in women with early-stage HER2-positive breast cancer.

1.4.6.1 Neratinib Single-agent Activity in Patients with HER2+ Breast Cancer

Early clinical data have demonstrated the activity of neratinib in patients who have already failed other small molecule or antibody-based HER2 targeted therapies. In the single-agent, first-in-human phase I study of neratinib in solid tumor, a 32% objective response rate (ORR) was observed among patients with trastuzumab refractory HER2+ disease [5]. Specifically, 8 of 25 patients had partial response (PR). Among the responders, two PRs occurred at neratinib doses of 120 or 180 mg per day, which was below the recommended monotherapy dose. All of these responders had prior trastuzumab therapy, notably six patients had received at least four trastuzumab-based therapies. Additionally, all had received prior anthracycline and gemcitabine, and the majority (7/8) had received prior taxane therapy. Six patients had also received prior capecitabine therapy.

An open-label, multicenter, Phase 2 study evaluated the efficacy and safety of neratinib 240 mg daily, in patients with and without prior trastuzumab treatment, who had advanced HER2+ breast cancer. The primary end point, the 16-week PFS rates, was 59% and 78% in prior trastuzumab-treated patients and trastuzumab-naïve cohorts, respectively [4]. The ORR was 24% and 56%, respectively, and the median PFS times were 22.3 and 39.6 weeks, respectively. Mean steady-state trough concentrations for the 240 mg daily dose exceeded concentrations needed to inhibit autophosphorylation of HER2 in preclinical models [18].

The most common adverse events (AE) were diarrhea, nausea, vomiting, and fatigue. Diarrhea was the most frequent Grade 3 to 4 AE, occurring in 30% of patients with prior trastuzumab treatment and in 13% of trastuzumab-naïve patients, which resulted in dose reductions of 29% and 4% of patients, respectively. However, treatment discontinuation (TD) occurred in only one patient due to diarrhea (Grade 2). No neratinib-related Grade 3 or 4 cardiotoxicity was reported. Additional information regarding previous clinical studies of neratinib for treatment of HER2+ breast cancer is provided in the current Investigator's Brochure.

Neratinib was also studied in combination with other agents such as trastuzumab (RR27%) [7], vinorelbine (RR 41% in lapatinib naïve patients) [1], paclitaxel (RR 71-77%)[2, 3], temsirolimus (RR 18%, CBR 82%)[9] and capecitabine (RR 57-64%) [8] in women with metastatic HER2 + breast cancers. A phase III clinical trial of neratinib for the extended adjuvant treatment of breast cancer (ExteNET trial) in early stage HER2-positive breast cancer showed promising DFS improvement of 33% compared with placebo ($p<0.0046$) (pending publication).

1.4.6.2 Neratinib in Activating Somatic HER2 Gene Mutated Breast Cancer (HER2 non-amplified)

Activating somatic mutations in the HER2 receptor have been identified in human breast cancers that lack *HER2* gene amplification by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). These patients are not candidates for HER2-targeted drugs under current standards of care due to lack of HER2 over-expression, but preclinical data had strongly suggest that these patients will benefit from HER2 targeted tyrosine kinase inhibitors. Neratinib could be an effective treatment option for breast cancer that carries an activating mutation in the HER2 gene [58]. Through cancer genome sequencing, HER2 activating somatic mutations have been identified.

Analysis of the data from eight breast cancer genome sequencing projects identified a total of 13 somatic HER2 mutations, including seven activating mutations such as G309A, D769H, D769Y, V777L, P780ins, V842I, and R896C[59]. These mutations of HER2 receptor are highly recurrent, with the most common mutations occurring in the residue 309-310 of the extracellular domain or the kinase domain [60]. Approximately 1.6% of all newly diagnosed breast cancers may harbor a HER2 mutation, and most of these patients do not have HER2 gene amplification or overexpression [59]. This percentage might be higher for patients who have relapsed. Interestingly, all functionally characterized mutations were sensitive to neratinib, including those that rendered cells resistant to lapatinib *in vitro* [59]. Additional HER2 mutations such as L755S were recently identified as a potential target for neratinib [61]. This provides the rationale for testing neratinib in patients with HER2 non-amplified breast cancer with identifiable HER2 activating mutations. Two clinical trials of neratinib for HER2-mutated metastatic breast cancer are currently enrolling patients (NCT01670877; NCT01953926).

We plan to include patients with these HER2-mutated breast cancers in this study. The following HER2 gene alterations identified through genomic sequencing (by CLIA certified lab) will fit the eligibility criteria:

Missense substitutions (G309A, S310F, S310Y, V659E, R678Q, L755S, L755P, E757A, D769H, D769Y, G776V, G776C, V777L, L841V, V842I, L869R, R896C); Insertions/deletions (A775_G776insYVMA, G776 insertions, G778_S779insCPG, P780_781insGSP,). (Refer to unpublished data provided by Puma Technology Inc.).

1.5 Aging and Decreased Tolerance of Chemotherapy

Aging brings about a progressive decrease in physiologic reserve that affects each individual at a unique pace [47, 48]. The age-related physiological decline in organ systems typically begins in the 3rd decade of life and is not evident at times of rest but becomes most apparent when the body is stressed. Either cancer or cancer treatment can be considered a physiological stressor, and the age-related decrease in physiologic reserve may affect tolerance to cancer treatment. Several studies have demonstrated that older adults are more likely to experience chemotherapy toxicity, and older adults are at greater risk for myelosuppression, cardiotoxicity, and mucositis[62, 63]. Older adults can, in most cases, tolerate chemotherapy in doses and schedules similar to those in younger adults, but side effects need to monitored closely and occasionally more aggressive prophylactic measures need to be employed [32].However, most studies to date have determined tolerability of cancer therapies in older adults retrospectively rather than using prospective interventional trials. With some therapies it has been suggested that a lower starting dose in older adults causes less toxicity and does not impact efficacy [35].

A number of age-related changes in drug absorption, distribution, metabolism, and excretion with aging may contribute to differences in treatment tolerance between older and younger patients. The absorption of drugs can be affected by decreased gastrointestinal motility, decreased splanchnic blood flow, decreased secretion of digestive enzymes, and mucosal atrophy[21, 36] With the increased use of oral therapy, medication compliance is an important issue as well. As a person ages, body composition changes, with an increase in body fat and decrease in lean body mass and total body water. The increase in body fat leads to a rise in the volume of distribution for hydrophilic drugs. In the population of older adults with cancer, malnutrition and hypoalbuminemia may result in an increased concentration of drugs that are albumin-bound [22].

Physiologic changes with aging, independent of disease, can affect the pharmacokinetics and pharmacodynamics of chemotherapy drugs. As one ages, there is a decrease in hepatic and renal mass. Autopsy studies demonstrate a decrease in liver volume with aging by approximately 25-50%. In addition, there is decreased hepatic blood flow, estimated at a 10-15% decrease in liver perfusion, even after taking into account the decrease in liver volume [22, 64]. Normal tissues may be less able to repair the molecular damage caused by antineoplastic agents due to cellular senescence, resulting in greater potential cardiac toxicity, neurotoxicity, mucositis, and hematologic toxicities [62]. And finally, there may be age-related changes in the biology of cancer which may impact the therapeutic efficacy and approach [25, 26]. These physiological changes with aging can affect drug disposition and tolerability to chemotherapy treatment in older patients. While several studies have demonstrated that older adults are more likely to experience chemotherapy toxicity [63, 65, 66], the comparative risk of targeted therapies has not been studied.

Older adults are an important population to study because 60% of all cancer cases and 70% of cancer mortality occur in patients over the age of 65[67]. Furthermore, the number of older adults with cancer is expected to rise significantly with the aging of the U.S. population. Older adults with cancer are also an understudied population. Accrual of older adults to clinical trials has been shown to be significantly lower than their proportion in the general population in both an analysis of SWOG trials [68] as well as in studies of drugs approved by the FDA over a seven year period [69]. Cancer patients age 70 or greater made up only 20% of participants enrolled in FDA registration trials from 1995 to 1999, though they made up fully 46% of the U.S. cancer population[15].

1.6 Factors Predicting Chemotherapy Tolerance

1.6.1 Measures of Biological Age

While certain declines in organ function are universal as the human body ages, the rate of this decline and the consequences on everyday function proceed at a unique pace in each individual. Therefore, a more detailed evaluation of older adult patients is needed in order to capture factors other than chronological age that predict for morbidity and mortality. A comprehensive cancer-specific geriatric assessment may serve this purpose, and includes an evaluation of functional status, other medical conditions, cognitive function, nutritional status, social support, psychological state, and a review of medications. Conclusions from several studies have emerged regarding the benefits of performing such an assessment. Interventions based on findings from such assessments have been shown to predict both survival[70] and toxicity of therapy[71].

Patients who undergo this assessment have also been shown to have better pain control and better mental health and well-being[72].

Among available clinical models, the Cancer and Aging Research Group (CARG) has developed a predictive model for chemotherapy toxicity that includes geriatric assessment variables, tumor and treatment variables, and laboratory values that independently predict chemotherapy toxicity in older patients with cancer[73]. In a CARG multi-center study, 500 older adults with cancer with a mean age of 73 years (range, 65 to 91 years) with stage I to IV lung (29%), GI (27%), gynecologic (17%), breast (11%), genitourinary (10%), or other (6%) cancer joined this prospective study. Patients were deemed by their treating oncologists to be "fit" for the treatment prescribed, and received chemotherapy at their oncologist's discretion. 53% of the enrolled patients experienced severe or life-threatening chemotherapy toxicities (Grade 3–5 toxicity as determined by the National Cancer Institute, Common Toxicity Criteria for Adverse Events), and among this group there was a 2% incidence of treatment-related mortality. A predictive model for grade 3 to 5 toxicity was developed that consisted of geriatric assessment variables, laboratory test values, and patient, tumor, and treatment characteristics. A scoring system in which the median risk score was 7 (range, 0 to 19) and risk stratification schema (risk score: percent incidence of grade 3 to 5 toxicity) identified older adults at low (0 to 5 points; 30%), intermediate (6 to 9 points; 52%), or high risk (10 to 19 points; 83%) of chemotherapy toxicity ($P < .001$). The assessment of "fitness" based on Karnofsky Performance Status (KPS) (Appendix B) did not adequately identify those at risk, but the CARG predictive model independently predicted the risk of toxicity[73].

Consensus statements now recommend the inclusion of a geriatric assessment as part of the evaluation of an older patient[74]. These tools, which include GA items, can be used to assess an older adult's risk of significant toxicity resulting from chemotherapy and assist with the discussion of treatment options between the oncologist and patient. However, the biological markers of aging were not included in these earlier studies. Therefore, there is an unmet need for evaluating blood-based biomarkers as a possible way to identify older adults at risk for chemotherapy toxicity and functional decline. In addition, these earlier studies focused on chemotherapy toxicity. The association of geriatric assessment and tolerance to biological targeted therapy is not adequately studied.

1.6.2 Biomarkers of Aging: Inflammatory Markers (IL-6, CRP) and a Coagulation Marker (D-dimer)

Elevated markers of chronic inflammation such as IL-6 and CRP, and a coagulation factor D-dimer correlate with aging and functional decline in geriatric patients. Expression of IL-6 and CRP increases with aging and can predict age-associated functional decline, increased morbidities and mortality [75-78]. Elevated levels of Il-6 and D-dimer at baseline were associated with subsequent functional decline and mortality in a cohort of 1723 older adults [79]. Furthermore, serum levels of CRP and D-dimer were associated with clinical frailty among 4,735 community-dwelling adults age over 65 [80]. In the context of cancer, elevated serum IL-6 correlates with more advanced cancer stage and poorer response to chemotherapy [81]. Plasma levels of CRP, which is considered one of the classic markers of systemic inflammation, increased rapidly in response to acute inflammation and are moderately increased in response to chronic inflammatory disease. Elevated CRP levels at the time of diagnosis of breast cancer are

associated with reduced overall and disease-free survival and with an increased risk of death from breast cancer [82]. Among patients with operable breast cancer, elevated plasma D-dimer levels were associated with lymphovascular invasion, higher clinical stage, and lymph node involvement [83]. Based on this growing evidence, we hypothesize that IL-6, CRP, and D-dimer may function as biomarkers of aging, potentially predict the risk of toxicity of cancer therapeutic in older adults with cancer.

As part of this study, we will evaluate the association of the geriatric risk score and biomarkers of aging (IL-6, CRP and D-dimer), with neratinib toxicity and PK.

1.7 Neratinib in the Older Patient Population Study Rationale

With the promising results from multiple clinical trials [1-9], neratinib has the potential to have a large impact on the delivery of targeted cancer treatment to the general population. There is significant interest in studying this drug among older adults as it is convenient to prescribe and easy to administer. However, neratinib appears to have all grades diarrhea rate of 92%. Grade 3-4 diarrhea was over 30% and dose reduction rate due to diarrhea were 20-53% across 9 trials of neratinib therapy (**Table 4**)[1-9]. This particular side effect is likely to have a great impact in the population of older adults. Due to high rates of all grades diarrhea, there is concern that without definitive studies in the older adult population, oncologists may have reservations in giving neratinib to elderly patients due to significant GI toxicities, especially diarrhea, or in dose reducing the agent without guidance. Currently, of 6 trials of neratinib study with a total enrollment of 291 patients, only 38 patients were 65 and older (PUMA Biotechnology Inc. provided data). We specifically designed this study to address this important area and develop strategies to effectively deliver this potent therapy to older patients.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

Table 4: Common Adverse Effects Occurring in Subjects Receiving Neratinib (N=476)*

System Organ Class	All Causality Frequency	Preferred Term	N=476	
			All grades N (%)	Grade 3/4 N (%)
Gastrointestinal disorders	Very common	Diarrhea	420 (88.2)	132 (27.7)
		Nausea	220 (46.2)	15 (3.1)
		Vomiting	169 (35.5)	19 (4)
		Abdominal pain (includes abdominal pain upper/lower, abdominal discomfort, abdominal distension)	170 (35.6)	9 (1.9)
	Common	Dyspepsia	33 (6.9)	0 (0)
Skin and subcutaneous tissue disorders	Very common	Dermatologic toxicities (includes rash, dry skin, pruritus, dermatitis acneiform, erythema, palmar-plantar erythrodysaesthesia syndrome, alopecia, nail disorder, and paronychia	206 (43.3)	0 (0)
General disorders and administration site conditions	Very common	Fatigue	160 (33.6)	14 (2.9)
		Asthenia	68 (14.3)	10 (2.1)

Metabolism and nutrition disorders	Very common	Decreased appetite	144 (30.3)	17 (3.6)
		Dehydration	52 (10.9)	18 (3.8)
Nervous system disorders	Very common	Headache	85 (17.9)	5 (1.1)
Blood and lymphatic disorders	Very common	Anaemia (includes haemoglobin decreased)	70 (14.7)	7 (1.5)
Investigations	Common	Aspartate aminotransferase (AST) increased	38 (8)	9 (1.9)
		Alanine aminotransferase (ALT) increased	38 (8)	12 2.5)

* Information provided via Investigator's Brochure

2.0 Specific Objectives and Goals

2.1 Primary Objective

To estimate the safety and tolerability of neratinib in adults age 60 or older with locally advanced or metastatic HER2 over-expressing breast cancer

2.2 Secondary Objectives

- To describe the full toxicity profile including all grade toxicities measured by NCI CTCAEv.4.0.
- To estimate the rate of all grades of GI toxicities such as diarrhea, nausea, and vomiting.
- To estimate the rate of dose reduction, delays and discontinuation related to study drug.
- To describe pharmacokinetic parameters of neratinib in adults 60 and older.
- To estimate overall response rate (ORR) and clinical benefit rate (CBR) defined by RECIST 1.1.
- To estimate event free survival (EFS), progression-free survival (PFS) and overall survival (OS).
- To evaluate the role of cancer-specific geriatric assessment tool in predicting treatment toxicities.
- To estimate adherence rate to neratinib in older adults (percentage of doses of neratinib taken).
- To explore the association of PK parameters and geriatric assessment findings.
- To explore if serum biomarkers of aging (IL-6, CRP, and D-dimer) are associated with treatment toxicities.

3.0 Study Endpoint

3.1 Primary Endpoint

Grade 2 or higher toxicities

3.2 Secondary Endpoints

- All grade toxicities as measured by NCI CTCAE v.4.0
- All grades of GI toxicities such as diarrhea, nausea, and vomiting
- dose reduction, holds and hospitalizations

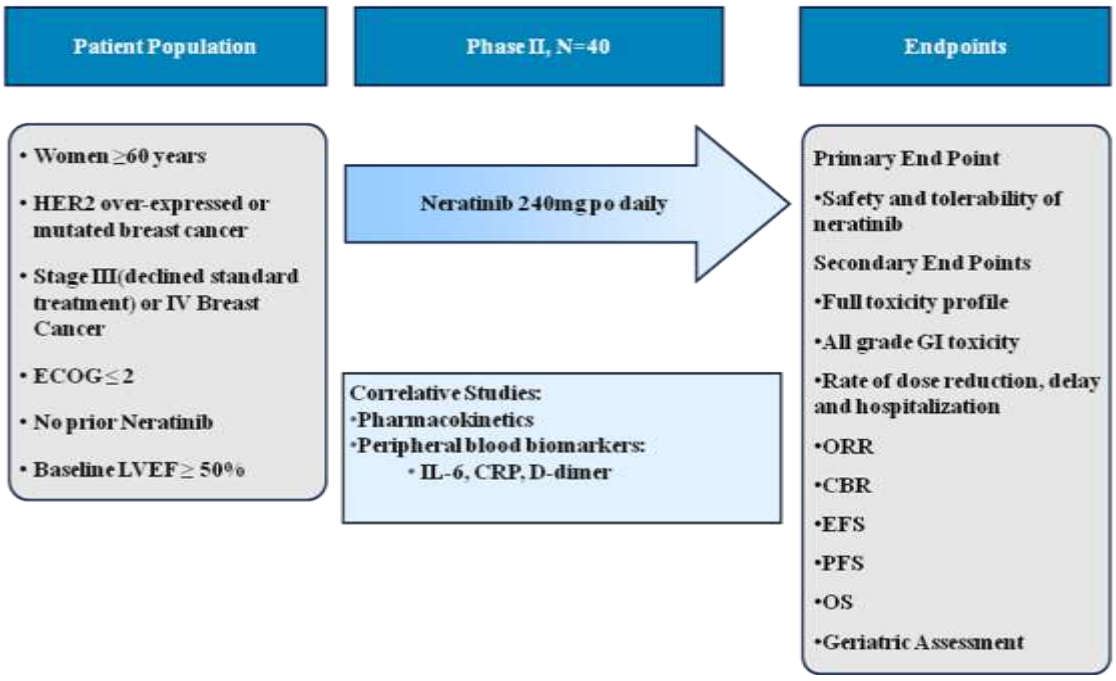
- Effect of age on PK parameters: clearance and volume of distribution and exposure-response relationships on efficacy and safety of neratinib
- Response as defined by RECIST
- EFS (where the event is toxicity or progression), PFS, OS
- Geriatric assessment score
- Adherence as defined by pill count
- IL-6
- CRP
- D-dimer

4.0 Study Design and Schema

The study will be an open label, single arm, phase II toxicity study of single agent neratinib in order to describe the toxicity profile in women age 60 and older with HER2 positive breast cancer. We plan to study 40 subjects, stratified by patient age (with at least 5 patients age 75 years or older, and no more than 15 patients 60-70, in order to assure that we study the entire age range of older adults). As diarrhea has been seen with neratinib, we have established additional guidelines and criteria which will be used to flag an unexpected number of patients that experience grade 3 diarrhea within the 2 cycles on neratinib treatment in the presence of aggressive mandatory anti-diarrhea management which will lead to a careful data review. There will also be one interim analysis of the toxicity profile after 20 subjects have been on drug for one cycle.

Patients are anticipated to participate in the study for an average of 48 months. This includes approximately 0.5 months for screening, an estimated average of 9.5 months for the active treatment phase, and an estimated average of 38 months for the long-term follow-up phase. Treatment is to be given for as long as it is tolerated and while there is no disease progression. Patients who permanently discontinue treatment will enter the long-term follow-up phase until death or withdrawal of consent.

The study schema is shown below:



5.0 Patient Eligibility

5.1 Inclusion Criteria

1. Female or male patient age ≥ 60 years.
2. ECOG performance 0-2 (see Appendix A for ECOG criteria)
3. Life expectancy of greater than 12 weeks.
4. Histologically or cytologically proven metastatic breast cancer (metastases can be proven with imaging results in certain circumstances provided that the initial tumor was demonstrated histologically).
5. Stage IV Her2/Neu positive breast cancer patients who failed previous anti-HER2 targeted therapies.
6. HER2 positivity as defined by ASCO/CAP guidelines.
7. If HER2 negative by IHC or FISH, but activating somatic mutations of HER2 gene identified through genomic sequencing including but not limited to the following (CLIA certified lab test): Missense substitutions (G309A, G309E, S310F, S310Y, S653C, V659E, R678Q, V697L, T733I, L755S, L755P, E757A, D769H, D769Y, D769N, G776V, G776C, V777L, L841V, V842I, R849W, L869R, R896C); Insertions/deletions (A775_G776insYVMA aka Y772_A755dup, G776VinsC, G776AinsVGC,G776 insertions, G778_S779insCPG, P780_781insGSP aka G778_P780dup, L755_T759del) and/or HER3 activating mutations. There is no limitation on the number of prior lines of systemic therapy or HER2-targeted therapies (prior neratinib not allowed).
8. Both measurable as well as non-measurable disease will be allowed.
9. Adequate organ and bone marrow functions defined below within 4 weeks of pre-registration:
    - Hemoglobin: ≥9g/dL (after transfusion, if necessary).
    - Total bilirubin: within normal institutional limits.

- AST (SGOT)/ALT (SGPT): ≤ 2.5 X institutional upper limit of normal.
- Creatinine clearance ≥ 30 mL/min as calculated by Cockroft-Gault formula.

10. Baseline left ventricular ejection fraction LVEF ≥ 50% as evaluated by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA).
11. All grade ≥2 toxicities other than alopecia from prior therapy have resolved by the time of study commencement.
12. Patient must have completed radiation therapy with adequate recovery of bone marrow and organ functions, before starting neratinib.
13. Patient with stable or treated brain metastases are eligible. Asymptomatic patients with metastatic brain disease who have been on a stable dose of corticosteroids for treatment of brain metastases for at least 14 days are eligible to participate in the study.
14. Provide written, informed consent to participate in the study and follow the study procedures.

5.2 Exclusion Criteria

1. Prior treatment with neratinib.
2. Concurrent usage of other investigational agents, chemotherapy, or hormone therapy. Prior chemotherapy, hormonal therapy, targeted therapy, and investigational agents are allowed but all toxicities grade ≥2 must have resolved by the time of study commencement (except alopecia).
3. Any major surgery ≤ 28 days prior to the initiation of investigational products.
4. Received chemotherapy or biologic therapy ≤ 3 weeks prior to the start of neratinib
5. Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2, including individuals who currently use digitalis specifically for congestive heart failure), unstable angina, myocardial infarction within 12 month of enrollment or ventricular arrhythmia.
6. Concurrent use of digoxin due to cardiac disease. QTc interval ≥450 milliseconds in men and ≥ 470 milliseconds in women within 2 weeks of registration or known history of QTc prolongation or Torsades de Pointes.
7. Inability to take oral medication
8. Other malignancy within the past 3 years with the exception of: a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) cervix or vulva carcinoma in situ; c) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder, or benign tumors of the adrenal or pancreas.
9. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (e.g., Crohn's disease, malabsorption, or Grade ≥2 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE v.4.0] diarrhea of any etiology at baseline).
10. Known clinically active infection with hepatitis B or hepatitis C virus.
11. Evidence of significant medical illness, abnormal laboratory finding or psychiatric illness/social situations that would, in the Investigator's judgment, makes the patient inappropriate for this study.

5.3 Inclusion of Women and Minorities

The study is open to everyone, regardless of gender or ethnicity. Although majority of the participant of this study is women, male patients who meet the inclusion criteria will be offered enrollment for participation. Efforts will be made to extend the accrual to a representative population, but in a trial which will accrue approximately 40 subjects, a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments and the need to explore gender, racial, and ethnic aspects of clinical research. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

6.0 Screening, Registration, and Follow-up Studies

6.1 Screening Procedures

6.1.1 General Guidelines

Eligible patients will be entered on study at the participating sites and centrally at the City of Hope Comprehensive Cancer Center. See **Appendix C** for Multicenter Guidelines. An Eligibility Screening Worksheet is attached as **Appendix G**.

Following registration, patients should begin protocol treatment after receiving the oral medication and after being told to do so by the study team. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Data Coordinating Center should be notified of cancellations as soon as possible.

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Studies or procedures that were performed within 2 weeks for clinical indications (not exclusively to determine study eligibility) may be used for baseline values, even if the studies were done before informed consent was obtained.

6.1.2 Procedure for On-study and Treatment Deviations

Any amendments to the study protocol need to be approved by the institutional review board (IRB) at both the study sponsor site as well as at all participating centers. All deviations or single subject exceptions to the study protocol must be reported to the primary IRB of the participating site, and to Dr. Yuan Yuan.

6.2 Informed Consent

The investigational nature and objectives of the trial, procedures and treatments involved, attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject and a signed informed consent will be obtained. Documentation of informed consent for screening will be maintained in the subject's research chart and medical record.

The participating clinicians who are approved at City of Hope must obtain informed consent and confirm in the electronic medical record that the patient has received the Notice of Privacy

Practice. This must be obtained before confirming eligibility, registration and the subject receiving any study treatment.

6.3 Participant Registration

6.3.1 COH DCC Availability and Contact Information

Eligible subjects will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope. DCC staff is available **between the hours of 8:00 a.m. and 5:00p.m. PST, Monday through Friday (except holidays).** DCC contact information is as follows:

- phone: (626) 256-4673 ext. 83968
- e-mail: DCC@coh.org

6.3.1 Slot verification and reservation

As the study nears completion of accrual, study team personnel (including physicians, protocol nurses and/or CRCs) may wish to contact the DCC to verify slot availability and to reserve an open slot or be placed in queue for slot opening. Slots may only be held for a limited time which will be determined by the PMT. The Data Coordinating Center should be notified of cancellations of prospective participants holding slots as soon as possible.

6.3.2 Registration procedure

To register a participant, the subsequent procedure is to be followed.

1. City of Hope staff or the participating institution's data manager/coordinator/research nurse should contact the DCC via telephone or email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly.
2. Documentation of current IRB approval must be on file with the DCC prior to registration of patients on this study for participating institutions.
3. The data manager/coordinator/research nurse should then e-mail copies to DCC@coh.org of the following documents to the DCC:
    - Registration Cover Sheet (Appendix N)
    - Completed Eligibility Criteria List (printed from Section 3.1-2 of the protocol)
    - Source documentation to support eligibility criteria**
    - Signed informed consent document
    - Signed HIPAA authorization form (if separate from the informed consent document)
    - Signed subject's Bill of Rights (COH only)

    **For COH participants, provide copies of source documentation only if not readily available as a finalized record in the COH EMR
4. After having received all transferred documentation, the DCC will complete the review the documents to verify eligibility, working with the COH staff and/or

participating institution as needed to resolve any missing required source elements. A subject failing to meet all protocol eligibility requirements will not be registered.

5. Once eligibility has been confirmed, DCC staff will register the participant by: assigning a subject accession number, register the subject on study centrally into MIDAS for all outside institutions (the COH CRC will directly accession into MIDAS), and enter the subject into the eCRF system, Medidata RAVE.
6. Once registration has been completed, DCC staff will send a Confirmation of Registration Form, including the participant study number and planned start date of treatment to:
    - the participating institution's study team: site PI, treating physician, protocol nurse, CRC and pharmacy.
    - the sponsor team: (Dr. Yuan, Dr. Blanchard, COH CRN and COH CRC).

6.4 Dose Assignment

Study patients will receive the same initial dose of study agents (see **Section 7.0**). Dose reductions can occur if medically necessary as described below (see **Section 8**).

7.0 Study Treatment Protocol

7.1 Treatment Overview

Treatment will be administered in an outpatient setting.

7.1.1 Neratinib

7.2 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 must be taken with food, in the morning. Neratinib is to be taken continuously in 28-day cycles, with no rest between cycles. Doses missed for toxicity will not be made up. Dose Adjustment

Management and dose modification associated with adverse events are outlined in **Section 8**.

7.3 Planned Duration of Therapy

The treatment will be continued until one of the following occurs:

- Progression of disease.
- Concurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s) as defined in Section 6 below.
- Patient decides to withdraw from the study.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

7.4 Criteria for Removal from Treatment

- Adverse Events.

- Current illness that prevents further administration of treatment.
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator.
- Clinical disease progression confirmed by imaging.
- Withdrawal of consent.

7.5 Subject Follow-Up

Throughout the study, reconciliation will be made between the amount of investigational product supplied, dispensed, returned, and subsequently destroyed or returned to IDS pharmacy. All investigational products that were supplied by the sponsor will be returned to IDS pharmacy, or destroyed at the site in accordance with COH guidelines. Individual patient dosing compliance should be reviewed at each study visit by study site staff. If patient non-compliance is noted, the patient should be re-instructed regarding proper dosing procedures in order to continue in the study. If repeated non-compliance is noted, additional steps may be taken, including withdrawal of the patient from the study. Subjects will be followed for toxicity outcomes for an additional 30 days after stopping the drug and until resolution of all grade >2 toxicities. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event, even after disease progression is noted. All patients will be passively followed until death, though active follow-up will cease upon removal from study.

7.6 Supportive Care, Other Concomitant Therapy, Prohibited Medications

All concomitant treatments, therapies and medications will be captured from the signing of the ICF until the end of the treatment. This will include the start date, stop date, generic name, route of administration, dose and indication for treatment. 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.

All concomitant medications taken during the study treatment will be recorded in the Case Report Form. The minimum requirements are drug name and dates of administration. All prescription and over-the-counter medications that have been taken within one month prior to the first dose of investigational treatment should also be reported in the Case Report Form. Patients should receive full supportive care during the study, including treatment with antibiotics, antiemetics, blood transfusions, antidiarrheals, and analgesics as appropriate, with the exception of drugs listed in **Section 7.6.3 and 7.6.4**.

7.6.1 Required Concomitant Treatment

7.6.1.1 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). Primary prophylactic use of antidiarrheal medication is **mandatory** for all enrolled patients in the neratinib study.

Loperamide is the recommended standard therapy to treat diarrhea in this study. If alternative antidiarrheal medication is proposed, this should be discussed with the PI and the reason documented in the source documents. Second-line antidiarrheal treatments and adjunctive

therapies (i.e., octreotide [SANDOSTATIN®]) (or equivalent as approved by the PI) are also recommended for use when appropriate.

All patients are required to receive intensive diarrhea prophylaxis:

- For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients 3 times a day (total 12 mg a day). The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.
- After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally twice a day (total 8 mg a day) through the first cycle of therapy (Day 28) from start of neratinib dosing.
- Thereafter, loperamide will be administered as needed (not to exceed 16 mg per day). The goal is to titrate to 1-2 bowel movements a day. Recommended loperamide dosing is listed below in **Table 5**.

Table 5: Loperamide Dosing

Day	Loperamide Dose
1	4mg at time of first dose of neratinib, then 12mg in 3 divided dose of 4mg tid
2-14	Daily dose of 12 mg in 3 divided doses of 4 mg tid
15-28	Daily dose of 8 mg in 2 divided doses of 4 mg bid
29+	Daily dose as needed (not to exceed 16 mg per day)

Patients must use a diary to record intake of loperamide. Loperamide pill counts will be conducted during the first 2 cycles (56 days) of therapy.

Loperamide Dose Adjustment:

Patients are expected to take loperamide prophylaxis as directed. However, patients may require individualization of loperamide prophylaxis dose (up to a maximum dose of 16mg per day) with the goal of titrating to 1-2 bowel movements a day.

- For patients who develop diarrhea during Cycles 1-2, loperamide should be increased up to a maximum of 16 mg a day.
- If a patient is unable to tolerate loperamide due to symptomatic constipation, loperamide should be held until after the first bowel movement and then resumed at a dose reduced by one level.
- For recurrent symptomatic constipation events, hold loperamide until after the first bowel movement and then resume at a dose reduced to the next lower dose level.
- If a patient is unable to tolerate once-daily loperamide due to constipation, hold loperamide and discuss subsequent loperamide dosing with the Medical Monitor.
- Neratinib dosing should continue if loperamide is held.

Recommended dose reductions for the -1 and -2 dose levels of loperamide are listed in **Table 6**.

Table 6: Loperamide Dose Reduction Levels for Constipation

Dose Level	Loperamide Dose	Tablets/Capsules per Day
0	4 mg TID	6 tablets/capsules a day
-1	4 mg BID	4 tablets/capsules a day
-2	2 mg TID	3 tablets/capsules a day
-3	2 mg BID	2 tablets/capsules a day
-4	2 mg once a day	1 tablet/capsule a day

Abbreviations: BID = twice daily; mg = milligrams; TID = three times daily

The Investigator/study nurse must review with the patient the **patient instructions (Appendix K)** for the management of diarrhea and the **Patient Diary (Appendix M)** for the patient's daily recording of investigational product during the first 2 cycles, number of stools, and use of loperamide and/or other anti-diarrheals. Both the patient and the Investigator/study nurse must sign the patient instructions for the management of diarrhea. 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 Investigator in the event of *de novo* onset or persistent Grade ≥2 diarrhea to discuss the appropriate course of treatment.

An "Optimal Management of Diarrhea Checklist" (**Appendix L**) will be reviewed and signed by study investigator or study nurse on Cycle 1 Day1. The study team will call patients at 1day, 2 days and 3 days after first dose of neratinib to assess tolerance.

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 anti-diarrheals, if applicable) noted on the diary for patients in the neratinib treatment 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. It is very important to initiate treatment with loperamide concomitantly with the first dose of neratinib to minimize occurrence and severity of diarrhea.

7.6.1.2 Prophylactic dosing instructions for Cycle 1

- Inform patients that they will experience diarrhea while taking neratinib. Administer loperamide:
    - For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients three times a day (total 12 mg a day). The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.
    - After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally twice a day (total 8 mg a day) through the first cycle of therapy (Day 28) from start of neratinib dosing.

    - Thereafter, loperamide will be administered as needed (not to exceed 16 mg per day).
    - The goal is to maintain the loperamide prophylaxis dose with a goal of titrating to 1-2 bowel movements a day.
- For patients who develop diarrhea during Cycles 1, loperamide should be increased up to a maximum of 16 mg a day.
- 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 PI).
- For Grade 2 diarrhea during Cycle 1 (4 to 6 stools per day above baseline, despite intensive loperamide): add lomotil 2.5mg every 6 to 8 hours, 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 Investigator). For persisting Grade 2 diarrhea during Cycle 1 despite the use of both immodium and lomotil: add octreotide as directed above.
- For Grade 3 diarrhea management during Cycle1: please refer to Table 7 and 8 for dose hold and reduction.
- For Grade 4 diarrhea management during Cycle 1: recommend permanently discontinue neratinib

The sites must contact the patient by phone at 1 day, 2 days, and 3 days after the first dose of neratinib:

- To inquire about any diarrhea and about potential AEs;
- To provide guidance to the patients for immediate and appropriate management of AEs, including diarrhea as specified in this protocol;
- To confirm that patient has loperamide available, in cased needed;
- To inquire about the first date of neratinib intake; the Investigator/research staff must update the electronic CRF (eCRF) within 3 days of receipt of this information.

(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 and the dose of anti-diarrheal medication taken each for the first 2 cycles.

7.6.1.3 New onset uncomplicated Grade 1 or Grade 2 diarrhea for Cycle 2 and beyond

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 Investigator).

7.6.1.4 For Grade 3 diarrhea with complicating features (dehydration and or hospitalization)

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). 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 PI).
- Administer octreotide (150 μg SC tid if dehydration is severe or at the treating physician's discretion, 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.

7.6.2 Permitted Concomitant Treatment

- Any palliative and/or supportive care for cancer-related symptoms, which are not otherwise specified in the list of prohibited medication, is permitted at the Investigator's discretion.

- Standard therapies for preexisting medical conditions, medical and/or surgical complications and palliation. All medication(s) as well as previous hormonal therapy, dose and length of therapy should be recorded in the CRF.

7.6.3 Concomitant Treatment Prohibited in Combination with Neratinib

The following treatments are prohibited throughout the duration of the active (treatment) phase of the study:

- Any concurrent chemotherapy, radiotherapy (including palliative radiotherapy), surgery related to cancer, anticancer immunotherapy, or other anticancer treatments including other investigational agents, megestrol and hormonal agents.
- Concurrent use of strong CYP3A4 inducers/inhibitors (**Appendix F**) should be cautiously monitored.

7.6.4 Other concomitant medications with potential for interaction

Concomitant administration of neratinib and P glycoprotein (P-gp) substrates with a narrow therapeutic window should be monitored closely with the exception of loperamide. Co-administration of neratinib with digoxin could result in increased digoxin levels and associated digoxin toxicity. Co-administration of digoxin while patient is on neratinib is prohibited. Refer to **Appendix D** for a list of substrates and inhibitors of P-gp.

Patients using drugs known to cause QT/QTc prolongation should be monitored closely with serial electrocardiograms (ECG) at the Investigator's discretion. Refer to **Appendix E** for a summary of drugs known to have a risk of causing QT/QTc prolongation, potentially causing Torsade de Pointes (TdP).

Patients should avoid agents known to be strong cytochrome P450 (CYP) 3A4 inducers or inhibitors (e.g., ketoconazole) for the duration of the active stage/phase of the study. Patients should also avoid grapefruit/grapefruit juice and herbal remedies, including St John's Wort. Refer to Appendix F for a list of inhibitors and inducers of CYP isoenzymes.

Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. If unavoidable, patients taking such agents should be monitored closely. Steroids given for physiological replacement, as anti-emetics, or inhaled, as well as short course of oral/topical steroids given for allergic reactions or asthma flares, are allowed.

Patients taking oral coumarin-derivative anticoagulants (i.e., warfarin) should be monitored closely and their anticoagulant dose adjusted as needed.

The solubility of neratinib is pH dependent and treatments that alter gastrointestinal pH such as proton pump inhibitors (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%. It is unknown whether separating PPI and a neratinib dose reduces the interaction. If an H2-receptor antagonist such as ranitidine 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 the neratinib dose should be separated by 2 to 4 hours.

7.6.4.1 Additional Studies

Geriatric assessment(GA):

The comprehensive geriatric assessment questionnaires are listed in **Appendix H (Self Geriatric Assessment Measure – Patient Questionnaire)** and **Appendix I (Healthcare Professional Questionnaire)**. As part of the study initiation, the study team (including PI, nurses, and CRAs) will be trained on the use of geriatric assessment questionnaires as well as potential interventions based on the results. The GA results will be made available to treating physicians and nurse. The individual treating physician will follow up on the GA results using their best clinical judgment. Furthermore, if a patient scores 11 or greater (a potential indicator of cognitive impairment) on the Blessed Orientation Memory and Concentration Test, the results will be reported to the treating physician so that further work-up and treatment can be performed as they deemed medically appropriate. Furthermore, if the patient endorses depression or anxiety (score great than or equal to 5), the doctor will be notified.

If patient's native language was not covered by the current language forms, Geriatric assessment form can be omitted with clear documentation.

PK and peripheral blood biomarkers:

Please refer to **Section 11** for PK and peripheral blood biomarkers correlative studies to be conducted under this protocol.

7.7 Laboratory Studies/Monitoring Studies

7.7.1 Required Clinical, Laboratory and Disease Evaluation at Baseline

Complete blood count and differential, comprehensive metabolic panel (including sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, and albumin), must be performed within 14 days of enrolling on trial.

A full history and physical exam including demographics, medical history, concurrent medications, vital signs, height measurement, weight measurement, and performance status analysis must be done within one week of enrolling on trial.

Radiologic evaluation including computed tomography (CT) of the chest, abdomen, and pelvis; or combined PET-CT with a diagnostic CT component, must have been performed within 30 days of study enrollment. If measurable disease is present, tumor measurements must be performed and reported from this scan. Central review is not required for treatment decisions in individual subjects.

The patient must complete a Geriatric Assessment prior to starting therapy (see Appendix I). If patient's native language was not covered by the current language forms, Geriatric assessment form can be omitted with clear documentation.

Cardiac imaging (either by echocardiogram or MUGA scan) with a reported left ventricular ejection fraction must be obtained within 30 days of study enrollment. Regardless of where the baseline evaluation is performed, future cardiac evaluation must be performed using only the

same modality as the baseline evaluation. A baseline EKG before starting treatment is also required.

7.7.2 Studies Obtained During the Trial

7.7.2.1 Disease evaluation

CT scans of the chest, abdomen, and pelvis; or PET-CT with a diagnostic CT component must be performed every 12 weeks (±1 week) in the absence of symptoms to document disease response or progression. In the presence of symptoms, these tests may be performed at the discretion of the treating physician.

7.7.2.2 Cardiac evaluation

Echocardiogram or MUGA scan must also be performed every 12 weeks (±1 week) in the absence of symptoms. The modality must be the same as the modality used in the baseline cardiac evaluation. In the presence of symptoms, or in the setting in which a prior study shows an abnormality requiring confirmation, echocardiogram or MUGA will be done at the discretion of the treating physician.

Complete blood count with differential and complete metabolic panel must be performed every four weeks (+/- 1 wk). If screening laboratories are performed within 14 days of the first study treatment, repeat laboratory tests will not be required before Week 1, Day 1.

7.7.2.3 Pharmacokinetics

Please refer to section 11.1 for details of sample collection, labeling, storage. Shipping, and analysis of PK samples.

7.7.2.4 Peripheral Blood Biomarkers Predicting Chemotherapy Tolerability

Please refer to section 11.2 for details of sample collection, labeling, storage and analysis of peripheral blood biomarker samples .

7.7.3 Monitoring Studies

7.7.3.1 Toxicity Evaluation

Because early toxicity is common during cycles 1 and 2 with neratinib, patients will have a focused visit with a study nurse to evaluate for new toxicities (Week 2, Week 3). A complete case report form is not required for these short visits, which are designed to ensure that interventions may occur should toxicity be apparent.

7.7.3.2 Adherence Evaluation

Adherence to neratinib will be measured by pill count every 4 weeks during the first five cycles during the investigator assessment, and every twelve weeks thereafter, as well as by patient self-report in dedicated patient diaries evaluated at the same time as pill count. In the event of discrepancy in these two measures of adherence, we will follow whichever indicates the lower measure of adherence (i.e. if patient states they took 26 of 28 doses, but only 20 doses are

missing, we will count the patient as having taken only 20 days. Alternatively, if 26 doses are missing, but the patient stated she only took 20 doses, we will count the patient as having taken only 20 doses.) All toxicity related dose interruptions or reductions, hospitalizations, and adverse events will be noted. Subjects will be followed for toxicity outcomes for an additional 30 days after stopping the drug, and until resolution of all grade >3 toxicities.

7.7.3.3 Geriatric Assessment

Geriatric assessment surveys will be administered at baseline(+/- 7 days), after every four cycles, cycle 4 day 1(+/- 7 days), cycle 7 day 1(+/- 7 days) and at the end of the study (+/- 7 days) if not performed in the previous month (see Appendix I for Geriatric Assessment Survey). If patient's native language was not covered by the current language forms, Geriatric assessment form can be omitted with clear documentation.

7.7.3.4 Survival Status

Patients will be followed indefinitely to establish overall survival. All participants enrolled on the study will be informed that their medical condition will be followed indefinitely. In order to obtain survival status on the enrolled patients we will need the patient's first and last name, middle initial, social security number, date of birth, and gender. This information will be securely transferred to the primary coordinating institution (City of Hope) and will be kept in a separate password protected file, which will only be linked for the purpose of establishing survivor status. The investigators will utilize the Social Security Death Index and the National Death Index to establish survival status. Survival analysis will be conducted once a year.

8.0 Dose Delays/Modifications for Adverse Events

Patients will be treated per protocol or until disease progression or withdrawal from treatment due to unacceptable adverse events or treatment consent withdrawal. At each study assessment, subjects are to be evaluated for evidence of drug-related adverse events.

In all cases where the subject is withdrawn due to unusual or unusually severe adverse event considered related to neratinib, the Investigator must report the withdrawal as a Serious Adverse Event.

Treatment may be delayed for up to 4 weeks, to allow for resolution of toxicity except in the event of those toxicities described below in which cases treatment must be discontinued permanently (see **Table 7**).

Recommended dose reductions for the -1 and -2 dose levels of Neratinib are listed as following:

Dose level	Neratinib
Starting dose	240mg
-1	160mg
-2	120mg

If a dose of neratinib is held, study procedures for that cycle will proceed on schedule as planned, without any delay. This also applies to tumor assessments, which should continue to be done every 12 weeks, starting from the first dose of neratinib until the first planned tumor assessment at 12 weeks (±1wk), and then after every subsequent 12 weeks (±1week) of treatment regardless of any changes in dose or occurrence of AEs. Missed dose(s) of neratinib (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 neratinib 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.

If a patient developed AE requiring dose reduction while on neratinib dose level of 120mg, neratinib will be discontinued.

8.1 General Toxicities

Detailed guidelines for dose adjustments of neratinib for general toxicities (exclude alopecia) are shown in **Table 7**. Grade 2 or 3 toxicities that are unrelated to neratinib will be excluded from the dose adjustment.

8.2 Gastrointestinal Toxicity

Neratinib dose adjustment guideline is listed in **Table 8**.

8.3 Pulmonary Toxicity

Guidelines for adjusting doses of neratinib in the event of pulmonary toxicity are shown in **Table 9**.

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 7: General Toxicities Requiring Dose Adjustment of Neratinib*

NCI CTCAE v.4.0	Action
Grade 3 adverse reaction	
1st appearance	Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at one dose level lower, lowest dose of neratinib is 120mg.
2nd appearance	Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at one dose level lower, lowest dose of neratinib is 120 mg
3rd appearance	Discontinue **neratinib** permanently.
Grade 4 adverse reaction	

Any	Discontinue **neratinib** permanently.

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

* Grade 2 or 3 toxicities that are unrelated to neratinib will be excluded from the dose adjustment.

Table 8: Gastrointestinal Toxicities Requiring Dose Adjustment of Neratinib

NCI CTCAE v.4.0	Actions
Grade 1 Diarrhea: Increase of **≤3** stools per day over baseline. OR **Grade 2 Diarrhea:** Increase of 4-6 stools per day over baseline. **Lasting ≤5 days**	Adjust antidiarrheal treatment per the guidelines for management of diarrhea at the first onset of diarrhea (refer to **Section7.6.1.1)**. Instruct patient to follow dietetic recommendations in the guidelines for management of diarrhea Fluid intake of ~2 L/day should be maintained to avoid dehydration.
Grade 3 Diarrhea: Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care and activities of daily living. **Lasting ≤2 days**	Adjust antidiarrheal treatment per the guidelines for management of diarrhea at the first onset of diarrhea (refer to **Section 7.6.1.1)**. Hold neratinib 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 neratinib at the next reduced dose level • Within 2-4 weeks after withholding treatment, reduce neratinib dose at the next lower dose. If event occurs a second time and the neratinib dose has not already been decreased, reduce neratinib dose to next lower dose level. If subsequent events occur, reduce the dose of neratinib to the next lower dose level. Once the event resolved to Grade ≤1 or baseline, start loperamide 4 mg with each subsequent neratinib administration.

Grade 3 Diarrhea: lasting >2 days despite treatment with optimal medical therapy, or associated with fever, dehydration OR **Any Grade 4 Diarrhea:** Life-threatening consequences: urgent intervention indicated. (would recommend d/c)	Recommend permanently discontinue neratinib OR if Investigator deems it to be in the patient's best interest to continue, hold **neratinib** until AE resolved to Grade ≤1; then resume **neratinib** at 120 mg.

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

Table 9: Pulmonary Toxicities Requiring Dose Adjustment of Neratinib

NCI CTCAE v.4.0	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 by one dose level 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.

8.4 Liver Toxicity

Guidelines for dose adjustment of neratinib in the event of liver toxicity are shown in **Table 10**.

Abnormal values in alanine transaminase (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.

8.5 Left Ventricular Ejection Fraction Toxicity

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

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 4 weeks and follow up cardiology consult.

Note that, for AEs other than asymptomatic LVEF decline, if neratinib is held for >28 days, the patient should be withdrawn from the active treatment phase of the study. 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.

Table 10: Liver Function Test Abnormalities Requiring Dose Adjustment of Neratinib

NCI CTCAE v.4.0	Actions
Grade 3 ALT (>5-20 x ULN) or Grade 3 bilirubin (>3-10 x ULN)	Hold **neratinib** until recovery to Grade ≤1 for patients with ALT Grade ≤1 at baseline. Evaluate alternative causes. For patients with ALT ≤ Grade 1 at baseline: Resume neratinib at the next lower dose level if recovery to ≤Grade 1 occurs within 4 weeks. If Grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue neratinib.
Grade 4 ALT (>20 x ULN) or Grade 4 Bilirubin (>10 x ULN)	Permanently discontinue **neratinib**. Evaluate alternative causes.
ALT >3 x ULN and Total bilirubin >2 x ULN and Alkaline phosphatase <2 x ULN (potential Hy's law indicators of drug-induced liver damage)	Hold **neratinib**. The patient should 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, 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. 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 investigator/sponsor immediately to discuss next steps, including evaluation of alternative causes, and management of investigational product. These events must be reported as SAEs.

NOTE: During evaluation of hepatotoxicity, bilirubin must be fractionated, PT must be measured, and liver imaging should be considered

Table 11: Left Ventricular Ejection Fraction (LVEF) Results Requiring Dose Adjustment of Neratinib for NYHA Level 1 (asymptomatic) or Level 2 (symptomatic) drop of LVEF.

Event on day of scheduled	Actions
Asymptomatic absolute decline of LVEF ≥10% from baseline OR LVEF<50%	A) If LVEF < 50%: Hold **neratinib** and seek Cardiology consult Recheck LVEF in a month, - If LVEF remains <50% or confirmed LVEF drop ≥ 10%, stop neratinib permanently; - If LVEF ≥ 50% and confirmed LVEF drop <10%, resume treatment and monitor LVEF every 12 weeks; B) If LVEF is ≥ 50%, but LVEF drop ≥10%, Hold neratinib and repeat LVEF in 4 weeks and follow step A C) If LVEF ≥ 50%, and LVEF drop <10%, continue neratinib
Symptomatic cardiac failure	**Neratinib** should be discontinued.

9.0 Data and Safety Monitoring Plan

Definition of Risk Level

This is a Risk Level 4 study as defined in the City of Hope Institutional Data and Safety Monitoring Plan [policy dated 07/09/2014]. This determination was made because the study involves a City of Hope held IND.

Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) is responsible for monitoring the data and safety of this study. The PMT consists of the Principal Investigator (PI), Collaborating Investigator, CRA/protocol nurse, and Biostatistician. The PMT is responsible for monitoring the data and safety of this study, including implementation of the stopping rules for safety and efficacy.

The PMT is required to submit periodic status reports (i.e., the PMT Report) according to the frequency prescribed in the City of Hope Institutional Data and Safety Monitoring Plan [policy dated 07/09/2014]. Important decisions made during PMT meetings only need to be noted in the PMT Report submitted to the Data and Safety Monitoring Committee (DSMC).

Protocol specific data collection will include the following items:

After 20 patients have completed one full cycle of therapy, the study team will review the data and assess the toxicity profile and rates of dose reduction, delays, interruptions and hospitalization related to the agent. Within this interim analysis, a specific review will be made of the data for the patients over 75 years of age. Additional guidelines will be used to flag an unexpected number of patients that experience symptomatic cardiac toxicity (NYHA Class III or

IV if cardiac failure, or Grade 3 or higher by NCI NCTAE v4.0 for other cardiac events), safety of neratinib in older adults (using CRFs based on CTCAE v.4.0), efficacy of neratinib in older adults (based on imaging using RECIST 1.1 criteria), geriatric assessment of older adults, adherence of the population to the oral medication, or cardiac safety in the study population (using cardiac imaging).

Adverse Events and Serious Adverse Events

The PI will be responsible for determining the event name, assessing the severity (i.e., grade), expectedness, and attribution of all adverse events.

Adverse Event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Reporting Non-serious Adverse Events – Adverse events will be collected after the patient is given the study treatment or any study related procedures. Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the PMT Report.

Serious Adverse Event (SAE) [Modified from the definition of unexpected adverse drug experience in 21 CFR 312.32] - defined as *any expected* or *unexpected adverse event*s that result in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Reporting Serious Adverse Events - begins after study treatment or any study related procedures. All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to the approved City of Hope's Institutional

policy [policy effective date: 05/14/14]. Serious Adverse Events that require expedited reporting will be submitted electronically using iRIS.

Adverse Event Name and Severity

The PI will determine the adverse event name and severity (grade) by using the CTCAE version 4.0. In addition, New York Heart Association (NYHA) Class III and IV heart failure will be captured.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Unexpected Adverse Event [21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Adverse Event Attribution

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Definite** - The AE is clearly related to the investigational agent or study procedure and unrelated to any other cause.
- **Probable** - The AE is likely related to the investigational agent or study procedure and unlikely related to other cause(s).
- **Possible** -The AE may be related to the investigational agent or study procedure and may be related to another cause(s).
- **Unlikely** -The AE is doubtfully related to the investigational agent or study procedure and likely related to another cause(s).
- **Unrelated** -The AE is clearly not related to the investigational agent or study procedure and is attributable to another cause(s).

COH Held IND

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the Medwatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

The PI or designee will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope's Institutional policy [policy effective date: 05/14/14].

Deviations and Unanticipated Problems
Deviation - A deviation is a divergence from a specific element of a protocol that occurred without prior IRB approval. Investigators may deviate from the protocol to eliminate immediate hazard(s) for the protection, safety, and well-being of the study subjects without prior IRB approval. For any such deviation, the PI will notify the COH DSMC and IRB within 5 calendar days of its occurrence via iRIS in accordance with the Clinical Research Protocol Deviation policy [policy effective date: 11/07/11].

It is not a deviation if the participants receive 80% of their assigned dose each cycle unless they have had a toxicity or the dose is modified.

Single Subject Exception (SSE)

An SSE is a planned deviation, meaning that it involves circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient. It is a deviation that is anticipated and receives prior approval by the PI and the IRB. The SSE must be submitted as a "Single Subject Exception Amendment Request" via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy [policy effective date: 11/07/11]. An IRB approved SSE does not need to be submitted as a deviation to the DSMC.

Unanticipated Problem (UP) – Any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Any UP that occurs during study conduct will be reported to the DSMC and IRB in accordance with the City of Hope's Institutional policy [policy effective date: 05/14/14] using iRIS.

COH Held IND

The Office of IND Development and Regulatory Affairs (OIDRA) will assist the PI in reporting the event to the Food and Drug Administration (FDA).

Reporting to Puma by the Principal Investigator

1. Principal Investigator (PI) or designee will inform Puma Pharmacovigilance of all SAEs that occur from the time of informed consent through 30 calendar days post last dose of neratinib, **regardless of attribution/ causality**.

   A completed MEDWATCH report will be emailed to Puma (PumaSAE@parexel.com) on or before the specified timelines listed below:

   - All expedited reports sent to the FDA will forwarded to Puma no later than seven (7) days for initial life-threatening and death reports, and fifteen (15) days for all other initial or follow-up serious and unexpected suspected adverse reaction (SUSAR), from the time of receipt of the SAE by Institution-Sponsor.

   - Any SAE that do not meet FDA's criteria for expedited reporting will be reported to Puma no later than thirty (30) days from the time of receipt of the SAE by Institution-Sponsor.

   - Should an Investigator be made aware of any SAEs occurring any time after the reporting period that may be causally related to the administration of neratinib, it should be promptly reported.

2. The PI or designee will report to Puma aggregate safety information every 3 months at the time of the COH PMT report.

Reporting to COH by Puma

During the Study and for a period of at least two (2) years following completion or early termination of the Study, Puma will report to Institution-Sponsor any new or unexpected information about the Study Drug that, in Puma's sole judgment, may pose a significant health or safety risk to Study Subjects or may influence the conduct of the Study.

10.0 Agent Information and Risks

10.1 Neratinib

10.1.1 Description

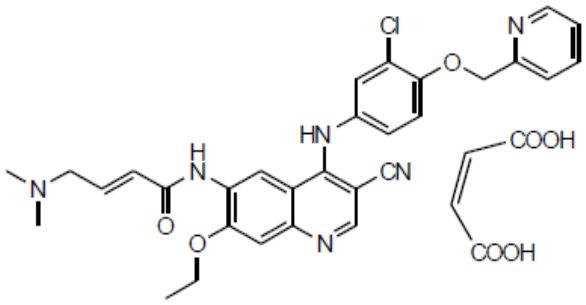
Generic Name/United States Adopted Name (USAN): Neratinib

Code Names: PB-272, HKI-272, HKI-272 maleate

Chemical Abstracts Service Indexed Name: 2-Butenamide,

N-[4-[[3-chloro-4-(2-pyridinylmethoxy) phenyl] amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-, (2*E*)-, (2*Z*)-2-butenedioate (1:1).

The molecular structure of neratinib maleate is shown below:



The physical, chemical, and pharmaceutical properties of neratinib maleate are listed in **Table 12**.

Table 12: Physical, Chemical, and Pharmaceutical Properties of Neratinib

Molecular Formula	C30H29ClN6O3·C4H4O4
Molecular weight	673.11
Appearance	Off-white to yellow powder
Solubility in water (room temperature)	0.4-0.5 mg/mL at pH 5.1
Dosage form	Capsules and tablets

Neratinib maleate has been provided as 40 mg immediate release tablets using common compendial excipients. Neratinib should be stored at 25°C (77°F) or below; do not freeze.

Excursions are permitted to 30°C (86°F). Neratinib should be stored with desiccant. Keep containers closed tightly.

10.2 Adverse Drug Reactions

Safety results from the completed and ongoing studies show that neratinib is generally well tolerated and has a consistent safety profile for subjects with breast cancer or other solid tumors. GI disorders accounted for the most frequently reported treatment related adverse effects (AEs). Diarrhea was the primary dose limiting toxicity (DLT) in the first in humans Phase 1 study. A pooled analysis of 476 subjects with advanced solid tumors who received neratinib monotherapy at dosages of 240 mg/day was performed, and the most common AEs were diarrhea (88.2%), nausea (46.2%), and vomiting (35.5%). The most commonly reported Grade 3 TEAEs were diarrhea (27.1%) and dyspnea (4.2%). Rash, which is associated with the use of other EGFR inhibitors, has been reported 17.4% of subjects treated with neratinib monotherapy.

10.2.1 Diarrhea and Other Gastrointestinal Toxicities

Diarrhea is the most frequent AE reported with neratinib, both as monotherapy and in combination with other drugs. In subjects with cancer, it is the most frequently reported AE leading to treatment discontinuation. Treatment-emergent diarrhea of all grades affected 88.2% of monotherapy subjects, and was Grade 3 or greater in 27.7%. There were 3 subjects (0.6%) who reported Grade 4 diarrhea events and there were no Grade 5 events (**Table 3**). The Grade 4 events occurred prior to the implementation of the intensive diarrhea management plan. Other specific event terms reported included gastroenteritis (1.1%), colitis (0.2%), enteritis (0.2%), and fecal incontinence (0.2%).

Diarrhea generally occurs early in the course of neratinib treatment. An intensive diarrhea management plan with prophylactic use of loperamide is being implemented for all ongoing and future neratinib clinical studies to reduce the frequency and severity of diarrhea within the first cycle of neratinib treatment. Among subjects receiving loperamide prophylactic antidiarrheal medication, 12-16% of subjects experienced Grade 3 diarrhea; no Grade 4 diarrhea were reported. In contrast, in studies without diarrhea prophylaxis, 28-32% of subjects experienced Grade 3 or Grade 4 diarrhea.

An updated prophylactic diarrhea management plan has shown promise in reducing the incidence and severity of diarrhea resulting from neratinib treatment. Preliminary results suggest that this plan, which has been implemented on all Puma-initiated clinical trials of neratinib, reduces the frequency of neratinib-related severe diarrhea events. In some cases, treatment interruption, dose reduction, antidiarrheal therapy, and, less frequently, treatment discontinuation may be necessary. Subjects with diarrhea complicated with vomiting, nausea, or anorexia need closer monitoring to ensure adequate hydration and the ability to ingest neratinib.

The intensive diarrhea management with prophylactic use of loperamide (**Section 7.6.1**) is anticipated to reduce or mitigate the occurrence of diarrhea complications, such as dehydration, and to markedly reduce the frequency of dose reduction or drug discontinuation episodes, thereby maximizing the likelihood that neratinib-treated subjects will remain on study-directed therapy beyond the first cycle of treatment.

Other frequent treatment-emergent GI disorders of all grades reported in monotherapy subjects include nausea (46.2%), vomiting (35.5%), and abdominal pain (21.8%) (**Table 4**). The toxicity grades of the vast majority of these events were ≤Grade 2 (61.2%).

Stomatitis is a general term that includes inflammation and ulceration of the mucosal lining of the mouth resulting from any cause. Oral mucositis is the more specific term that is used to describe oral mucosal inflammation and ulceration induced by cancer therapies. In general, stomatitis events have been reported in 10.7% of subjects who received neratinib as monotherapy. The toxicity grades of the vast majority of the events are Grade 1 (9.2%) and Grade 2 (1.3%). One (1) subject had a Grade 3 mucosal inflammation that resolved with treatment. There were no Grades 4 or 5 and none were reported as serious adverse events. About 84% resolved without neratinib dose interruption or discontinuation and about 6% resolved with treatment interruption. Specific event terms reported included stomatitis (4.6%), mucosal inflammation (3.8%), mouth ulceration (1.3%), aphthuous stomatitis (0.8%), mucosal ulceration (0.2%), and oral mucosal blistering (0.2%).

10.2.2 Dermatologic Toxicities

Dermatologic toxicities associated with EGFR inhibitors include rash, dryness of the skin and mucus membranes, hair changes and alopecia, nail changes, and hand and foot reactions. EGFRs are expressed in epidermis, the sweat glands, and hair follicles of the skin. EGFR inhibitor-induced toxicity is believed to be caused by an increase in keratinocyte production that occludes skin follicles and impairs their differentiation which causes the outer layers of the skin to shed, decreasing skin thickness [84] . Dry skin (xerosis) occurs as a consequence of abnormal keratinocyte differentiation, which disrupts thestratum corneum and sebaceous production impairing the ability of the epidermis to retain water [85]. Extreme dryness and erythema causes fissuring or ulceration of the skin [86].

Skin and subcutaneous tissue disorders have been reported in 43.7% of subjects who received neratinib as monotherapy. Rash in general has been reported in 19.3% of subjects including 14.5% reported as Grade 1; there were no events ≥ Grade 3. Specific event terms reported included rash (17.4%), rash pustular (0.8%), rash erythematous (0.6%), rash maculo-papular (0.4%), rash follicular (0.2%), rash generalized (0.2%), and rash pruritic (0.2%).

Additional dermatologic toxicity event terms reported included dry skin (8.6%), pruritus (6.3%), dermatitis acneiform (5.3%), erythema (4%), palmar-plantar erythrodysesthesia (PPES, i.e. hand-foot syndrome, 3.2%), alopecia (3.2%), skin fissures (2.3%), acne (1.5%), eczema (1.3%), skin ulcer (1.3%), hyperhidrosis (1.3%), night sweats (1.1%), skin exfoliation (1.3%), skin lesion (1.1%), and dermatitis (0.8%). Among subjects who received neratinib monotherapy at 240 mg/day (N=476), PPES has been reported in 3.2% of subjects; the majority of PPES events were Grade 1 (1.5%) and Grade 2 (1.7%).

Alopecia has been reported in 3.2% of subjects who received neratinib as monotherapy, the majority of which were Grade 1 (2.5%).

Paronychia has been reported in 4% of subjects who received neratinib as monotherapy, the majority of which were Grade 1 (2.9%), and none were reported as serious.

10.2.3 General Disorders (Fatigue and Asthenia)

Fatigue has been reported in 33.6% of subjects who received neratinib as monotherapy. The majority of fatigue AEs was reported as Grade 1 (19.1%), Grade 2 (11.6%), and Grade 3 (2.9%); none were Grade 4 or 5.

Asthenia has been reported in 14.3% of subjects who received neratinib as monotherapy, and the majority of those AEs were reported as Grade 1 (7.4%) and Grade 2 (4.8%).

10.2.4 Metabolic and Nutritional Disorders (Decreased Appetite and Dehydration)

Many forms of cancer present with a complex metabolic profile characterized by loss of lean body mass known as cancer cachexia. Decreased appetite characteristic of cancer cachexia is common in subjects with cancer. Approximately half of all subjects with cancer experience cachexia with prevalence as high as 86% [87].

Decreased appetite has been reported in 30.3% of subjects who received neratinib as monotherapy. Dehydration as a complication of diarrhea has been reported in 10.9% of subjects on neratinib monotherapy, in particular, when diarrhea is associated with nausea and vomiting. The vast majority of these events were ≤Grade 2 (7.1%).

10.2.5 Nervous System Disorders (Headache)

Headache is one of the more common side effects of TKIs reported in as much as 37% of subjects treated with imatinib and nilotinib[88] [89]. Headache has been reported in 17.9% of subjects who received neratinib as monotherapy. The majority of headache AEs was Grade 1 (14.3%), and the majority was reported as non-serious.

10.2.6 Hematologic Toxicities

Overall, hematologic toxicities have been reported in 20.6% of subjects who received neratinib as monotherapy. It is subdivided into 3 categories: anemia, leukopenia and neutropenia, and thrombocytopenia. Leukopenic and neutropenic events have been reported in 10.3% of subjects who received neratinib as monotherapy. The vast majority of the reports were ≤Grade 2 (8.8%). Specific event terms reported included lymphopenia (4.6%), leukopenia (3.2%), neutropenia (3.2), WBC count decreased (1.5%), febrile neutropenia (0.2%), and neutrophil count decreased (0.2%). Thrombocytopenia has been reported in 1.7% of subjects who received neratinib as monotherapy.

Neratinib preclinical data from a 1-month and a 6-month toxicity study in rats showed decreases in parameters of red cell mass (RBCs, hemoglobin, and hematocrit, 4% to 9%). In the clinical setting, 19.1% of subjects on neratinib monotherapy presented treatment-emergent blood and lymphatic disorders, of which, 3.3% comprised Grade 3 and 4 events (there were no Grade 5 events). The most frequently reported event was anemia (10.9%), the majority of which were Grade 1 (5.7%) and Grade 2 (4%), with 1.3% of subjects reporting Grade 3/4. In addition, decreased hemoglobin has been reported in 3.8% of subjects who received neratinib monotherapy, the majority of which were Grade 1 (2.3%) and Grade 2 (1.3%).

10.2.7 Hepatotoxicity

In general, hepatotoxicity events have been reported in 18.1% of subjects who received neratinib as monotherapy. Specific event terms reported included ALT increased (8%), AST increased (8%), blood alkaline phosphatase increased (6.9%), gamma-glutamyl transferase (GGT) increased (3.4%), hypoalbuminaemia (2.3%), hyperbilirubinaemia (1.7%), ascites (0.8%), transaminases increased (0.8%), blood bilirubin increased (0.4%), hepatic failure (0.2%), hepatic function abnormal (0.2%), hepatic pain (0.2%), jaundice (0.2%), and varices oesophageal (0.2%). The vast majority of these events were ≤Grade 2 (12.8%) with a few Grade 3 (4.8%) and 1 subject (0.2%) who had Grade 4 events.

10.2.8 Pulmonary Toxicity

Dyspnea has been reported in 16.8% of subjects who received neratinib as monotherapy, the majority of which were Grade 1 (6.1%) and Grade 2 (4.4%). Uncommon reports of lung infiltration (0.2%) and pneumonitis (0.2%) have been received in subjects treated with neratinib as monotherapy. Both events were reported as Grade 1. Patients receiving neratinib should be monitored for acute onset or worsening of pulmonary symptoms such as dyspnea, cough, and fever, and treated appropriately.

10.2.9 Cardiac Toxicities

Overall, cardiac toxicities have been reported in 12.6% of subjects who received neratinib monotherapy. Cardiac toxicities are divided into 3 categories: cardiac arrhythmia, cardiac failure, and ischemic heart diseases.

Cardiac Arrhythmia events have been reported in 3.6% of subjects who received neratinib monotherapy. The majority of the events were ≤Grade 2 (3.1%). Specific event terms reported included palpitations (1.1%), tachycardia (0.8%), arrhythmia (0.6%), syncope (0.6%), loss of consciousness (0.4%), bradycardia (0.2%), and electrocardiogram abnormal (0.2%) (Data provided thorough Neratinib IB).

Cardiac Failure events have been reported in 6.9% of subjects who received neratinib as monotherapy. Specific events reported included oedema peripheral (4.6%), oedema (1.1%), ejection fraction decreased (0.6%), left ventricular dysfunction (0.4%), cardiac failure (0.2%), and cardiopulmonary failure (0.2%). The majority of the reports were ≤Grade 2 (6.6%) (**Table 13**). Guidelines for dose adjustments of neratinib in the event of abnormalities in LVEF are provided in study protocols, which include withholding treatment if LVEF is below 50% and discontinuation of treatment for symptomatic cardiac failure. Subjects receiving neratinib should be monitored for the development of signs and symptoms of congestive heart failure and evaluated appropriately.

Ischemic Heart Disease events have been reported in 3.8% of subjects who received neratinib as monotherapy. Specific event terms reported included blood creatine phosphokinase increased (1.9%), electrocardiogram T wave abnormal (0.4%), coronary artery stenosis (0.2%), electrocardiogram T wave inversion (0.2%), troponin I increased (0.2%), and troponin increased (0.2%). The majority of these events are ≤Grade 2. Four (4) cases of angina pectoris (0.8%) have been observed in subjects on neratinib monotherapy; all cases were ≤Grade 2 and were non-serious. In addition, 1 non-serious Grade 2 subendocardial ischemia and 1 serious Grade 4 acute myocardial ischaemia have also been reported (Neratinib IB).

Table 13. Summary of LVEF Abnormalities, Shift from Baseline in % by Worst On-study Value, Occurring in Subjects With Advanced Solid Malignancies Receiving Single-agent Neratinib (240 mg, All Subjects, Safety Population, Pooled Studies)

	Number of Subjects (N =476) Worst LVEF% On-Study			
Baseline LVEF	**<45% n (%)**	**45%-50% n (%)**	**50–55% n (%)**	**≥55% n (%)**
<45%	0	0	0	0
45-50%	0	0	3 (0.6)	0
50-55%	1 (0.2)	4 (0.8)	14 (2.9)	9 (1.9)
>=55%	5 (1.1)	3 (0.6)	35 (7.4)	299 (62.8)

11.0 Correlative/Special Studies

11.1 11.1 PK Analysis

A population pharmacokinetic-pharmacodynamic analysis of neratinib efficacy and tolerability endpoints will be performed in this patient population to assess the variability of neratinib concentrations among individuals in the target patient population. Blood samples will be collected, processed and stored until analysis.

PK samples will be collected at the following time points: Cycle 1 Day 15 pre-dose (± 20minutes), 6 hours post-dose (60 minutes) and Day 1 Cycle 3 and Day 1 Cycle 4 pre-dose (± 20 minute) (Table 14). All pre-dose samples should be collected within 30 minutes before the daily dose. Patients will be instructed to record the exact time to the minute that the dose was taken on these days. In the event that the neratinib dose is held or the dose level is changed, pharmacokinetic sample will be rescheduled accordingly.

Table 14. PK Sample Collection Time Points

PK sample collection	Cycle 1 Day 15 (±1day)	Cycle 3 Day 1 (±3days)	Cycle 4 Day 1 (±3days)
Collection time	Pre-dose (± 20 minutes); 6 hours post-dose (±60 minutes)	pre-dose (± 20 minutes).	Pre-dose (± 20 minutes).

At each of the required time points, 10 mL venous blood will be collected into a tube containing K2EDTA. Samples will be inverted several times and kept on ice until processing can begin. Plasma will be separated from whole blood by centrifugation at 1,500 x g for 10 minutes at 4° C and ten approximately equal aliquots (300 uL minimum) will be transferred to appropriately-labeled polypropylene tubes and maintained on wet ice until frozen at ≤ -70°C until shipping. Specimens will be batched at each participating site and stored in freezers at each site. At City of Hope, the specimens will be stored in a freezer accessible only to members of the City of Hope pharmacokinetic staff working under the auspices of Tim Synold, PharmD. Each tube will be labeled with the study number, patient registration number, time point, and the date and time the sample was drawn.

At end of study, a shipment of frozen serum samples at each site will be packed in the shipping container in sufficient dry ice to last at least 3 days (typically 6-8 kg). The container will be sealed and shipped along with the packing worksheet via courier to:

Covance Bioanalytical
3301 Kinsman Blvd.
Madison, Wisconsin 53704-2523;
Phone: (608) 230-1691

Concentrations of neratinib will be measured in plasma with a validated assay method.

NONMEM, a statistical software program that uses non-linear, mixed effects models to determine PK parameters (clearance and volume of distribution), the inter- and intra-patient variability and the population variability in the parameter estimates will be used for this analysis. Random sources of error, intrinsic factors (e.g., age, sex, race, body weight, liver function and renal function) and extrinsic factors (e.g., concomitant medications such as proton pump inhibitors, digoxin, or anti-infectives) will be evaluated to identify factors that contribute to the observed variability in the PK parameter estimates.

A population pharmacokinetic-pharmacodynamic analysis of neratinib efficacy and tolerability endpoints will be performed in this patient population. The final PK data will be used to generate post-hoc neratinib patient-level plasma PK profiles, from which patient-level neratinib area under the curve (AUC) and maximum plasma concentration (Cmax) exposure metrics will be estimated. Neratinib dose and estimated AUC and Cmax exposure metrics will then be used to complete an exploratory data analysis of potential exposure-response relationships for efficacy and safety endpoints.

11.2 Peripheral Blood Biomarkers Predicting Chemotherapy Tolerability

Peripheral blood biomarkers (IL-6, CRP, D-dimer) analysis will be performed on samples collected at baseline after 3 cycles, and at end of study when patient receives geriatric assessment. At each of the required time points, two tubes of venous blood (10 mL) will be collected into a K2EDTA tube (purple top) and will be transported on ice to Dr. Timothy Synold's laboratory in the 1st floor of the Shapiro Clinical Research Bldg., Room 1042., one for peripheral blood biomarkers and one for ctDNA. A medical log will be kept in each laboratory, to be filled out by the deliverer of the samples, and signed off by a member of Dr. Synold's lab. A receipt will be made and stored in the patient's chart for future record keeping. This will ensure safety and proper identification of the sample. Plasma will be separated from whole blood by centrifugation at 1,500 x g for 10 minutes at 4° C and transferred to appropriately-labeled polypropylene tubes and frozen at ≤ -20°C. Specimens will be batched at each participating site and stored in freezers at each site. At City of Hope, the specimens will be stored in a freezer accessible only to members of Dr. Synold's laboratory. Each tube will be labeled with the study number, patient registration number, time point, and the date and time the sample was drawn.

Peripheral blood biomarkers (IL-6, CRP, D-dimer) analysis will be performed on samples collected at baseline after 3 cycles, and at end of study when patient receives geriatric assessment. Methods for measuring the three biomarkers are well established with enzyme-linked immunosorbent assays. For plasma biomarker measurement, 7.5 ml peripheral blood is

collected prior to initiation of chemotherapy. Plasma is stored at -80 ºC until assays are run. Quantitative IL-6 and CRP levels will be obtained using NOVEX® immunoassay (Invitrogen) and D-dimer levels will be measured with Nanopia® D-dimer (Sekisui).

Circulating DNA fragments carrying tumor-specific sequence alterations (ctDNA) are found in the cell-free fraction of blood, representing a variable and generally small fraction of the total circulating DNA. Advances in sequencing technologies have enabled the rapid identification of somatic genomic alterations in individual tumors, and these can be used to design personalized assays for the monitoring of ctDNA. Studies have shown the feasibility of using ct DNA to monitor tumor dynamics in a limited number of patients with various solid cancers, but few cases of breast cancer have been analyzed [65].

11.3 Specimen Labeling and Shipping

Tubes containing plasma samples must be clearly labeled, preferably with a printed label containing the following information:

1) An anonymized number that clearly indicates the site at which the sample was accrued and processed. For example, samples from City of Hope could be labeled COH001, COH002 etc. The Synold lab wishes to remain blinded throughout the duration of this study. Therefore, it is the responsibility of each site to maintain a record of the anonymized sample numbers sent to the Synold Lab and the patient ID#'s linked to them.
2) Date and time when the patient's blood draw was performed.
3) The IRB Protocol # associated with the collection of the sample.

Every 4 months, frozen plasma will be shipped from participating sites to Dr. Synold's laboratory at City of Hope. The specimens will be shipped via FedEx Priority Overnight® on dry ice to ensure the specimens remain frozen during transportation.

Dr. Timothy Synold
Clinical Immunobiology Correlative Studies Laboratory (CICSL)
Shapiro Building Room 10-12-1044
City of Hope Comprehensive Cancer Center
1500 East Duarte Rd.
Duarte, CA 91010

11.4 Bacteriomic Profiling

11.4.1 16S Gut Microbiome rRNA analysis

Fecal samples are relatively easy to collect and non-invasive. They provide an indication of the gut microbiome which may be an indicator of general health, impact drug availability, and indicate the presence of communities associated with inflammation, digestive inefficiencies, and pathogens. Monitoring the gut microbiome may allow us to predict the risk of possible side effects of targeted therapy (colitis and decreased appetite) and therapeutic efficacy

The exploratory objective to monitor the gut microbiota at baseline, on treatment and end of treatment using fecal samples. The differences in gut microbiota within and between fecal samples will be compared using alpha and beta diversity metrics based on 16S rRNA sequencing.

11.4.2 Stool Specimen Collection

Fecal material will be collected in a Zymo Research DNA/RNA Shield Fecal Collection Tube by patients as instructed. A standard operating procedure (SOP) has been generated for stool collection, as outlined in Appendix O. Stool collection kit contents are listed in Appendix Q. A copy of this SOP will be provided to the patient and their understanding of the SOP will be documented by the PI.

Samples will be collected pre-treatment (within 7 days prior to start of Neratinib), C1Day 15 (+/-3 days), C2Day1 (+/-3 days), C2Day15 (+/-3 days), C3Day1 (+/-3 days). Patient will bring samples on the scheduled study visits.

All samples will be collected by participants at home or during study visit. Study team will collect the samples and transport to Biospecimen Coordinator in COH Biorepository.

12.0 Experimental Design Schema

	Pre-Study (up to 28 days prior to enrolling)[i]	Cycle 1 Day 1 (28 day cycle)	Cycle 1 Day 8 (± 1 day)	Cycle 1 Day 15 (± 1 day)	Cycle 2 Day 1 (± 3 days)	Cycle 2 Day 15 (± 3 days)	Cycle 3 Day 1 (± 3 days)	Cycle 4 Day 1 (± 3 days)	Cycle 5 Day 1 (±3 days)	Cycle 6 Day 1 (±3 days)	Every Cycle Thereafter (± 3 days)	Every 3 cycles (±7 days)	Off Treatment[h]
Neratinib (day 1-7 of each wk) [a,b]		X	X	X	X	X	X	X	X	X	X		
Demographics	X												
Medical history	X												
Concurrent meds (± 1 wk)	X	X			X		X	X	X	X	X		X
Physical exam (± 1 wk)	X	X			X		X	X	X	X	X		X
Vital signs (± 1 wk)	X	X			X		X	X	X	X	X		X
Height	X												
Weight (± 1 wk)	X	X	X	X	X	X	X	X	X	X	X		X
Performance Status (± 1 wk)	X	X			X		X	X	X	X	X		X
CBC w/diff, plts (± 1 wk)	X	X			X		X	X	X	X	X		X
Complete Metabolic Panel[c] (± 1 wk)	X	X	X	X	X	X	X	X	X	X	X		X
Diarrhea Checklist		X[l]											
Nurse brief toxicity evaluation		X	X	X	X	X	X						
EKG	X												
Pharmacokinetic samples [j]				X			X	X					
Adherence evaluation (pill count, diaries) (± 1 wk)		X	X	X	X	X	X	X	X	X	X		
Adverse event evaluation (± 1wk)		X	X	X	X	X	X	X	X	X	X		X
Tumor measurements using CT or PET-CT (± 1 wk)	X[d]							X				X[e]	X[f]
LVEF Assessment	X[d]							X[e]				X[e]	X[f]
Geriatric Assessment Survey(±1 wk) [k]	X							X					X[g]
Peripheral Blood Correlatives[k]	X							X					X
Bacteriomic profiling	X[m]			X	X	X	X						

a: Dose as assigned; neratinib 240mg orally daily; Doses held due to toxicity will not be made up.
b: If baseline laboratory tests are done within 14 days of start of treatment, these labs do not need to be repeated prior to Day 1.
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
d: Baseline assessment may be done up to 30 days prior to study enrollment.
e: Tumor measurements and LVEF assessment are repeated every 3 months ± 1 wk until patient comes off study. Documentation (radiologic or clinical) must be provided for patients removed from study for progressive disease.
f: Off-study radiologic evaluation will only be done if clinically indicated.
g: Geriatric assessment will be performed at baseline prior to study, after 3 cycles (±7 days) and at end of study (±7 days). Geriatric assessment will be repeated off study ONLY if it had not been administered within the previous month. If patient's native language was not covered by the current language forms, Geriatric assessment form can be omitted with clear documentation.
h: Patients will be followed for 30 days following discontinuation of therapy in order to capture toxicity attributable to therapy.
i. Chart review data must be within 28 days to determine if patient meets study criteria. Once patient meets study criteria, then all criteria must be within window specified in protocol from Day 1 as indicated in column one in the schema above.
j: Pharmacokinetics samples will be collected at the following time points: Cycle 1 Day 15 pre-dose (± 20 minutes) and 6 hours post-dose (± 60 minutes); pre-dose (± 20 minutes) on Cycle 3 Day 1 and Cycle 4 Day 1.All pre-dose samples should be collected within 30 minutes before the daily dose in 10 ml purple-top tube.
k: Peripheral blood correlatives for inflammatory marker measurement (IL-6, CRP and D-dimer) and ctDNA will be collected in 10 ml purple-top tube at baseline, after 3 cycles (Cycle 4 Day 1 ± 7days), and at end of study (±7days) when patient receives geriatric assessment.
L: An "Optimal Management of Diarrhea Checklist" will be reviewed and signed by study investigator or study nurse on Cycle 1 Day1. The study team will call patients at 1day, 2 days and 3 days after first dose of neratinib to assess tolerance.
m. Stool samples must be collected within 7 days prior to start of neratinib, C1Day 15 (+/-3 days), C2Day1 (+/-3 days), C2Day15 (+/-3 days), C3Day1 (+/-3 days).

13.0 Endpoint Evaluation Criteria/Measurement of Effect

13.1 Response Criteria

For the purposes of this study, patients should be reevaluated for response every 12 weeks. Response and progression will be evaluated in this study using the new updated international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee version 1.1. Per the RECIST criteria, as disease response is not the primary endpoint of this trial, confirmatory scans following documentation of progression or response will not be required. Rather, progression/response will be determined based on results of the single scan.

Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with Neratinib.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

13.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >10mm with conventional techniques (CT, MRI, or caliper measurement) and as >20mm by chest X-ray (if clearly defined and surrounded by aerated lung.) Lymph nodes greater than 10mm on short axis are considered measureable as well. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <20 mm by chest X-ray or <10 mm using CT, MRI or caliper measurement), are considered non-measurable disease. Organomegaly, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI) are all non-measurable.

Target lesions: All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Lymph nodes less than 15mm in the short axis cannot be used as target lesions. 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). A 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.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 10 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.

13.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US): When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

13.4 Response Criteria

13.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Lymph node CR is when the lymph node has decreased to less than 10mm in the short axis.

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 the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (including the baseline scan if that is the smallest), and at least a 5mm increase or the appearance of new lesions.

Stable Disease (SD): 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.

13.5 Evaluation of Non-Target Lesions (see Table 15)

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Incomplete Response (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. However, unequivocal progression should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of non-target lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances.

13.5.1 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 the smallest measurements recorded since the treatment started as reference for progressive disease). The patient's best response assignment will depend on the achievement of measurement criteria, but confirmation is not necessary.

Table 15: Assessment of Best Overall Response Using Target and Non-Target Lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note : Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as ―symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

13.6 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 recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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 Progression-free Survival

Progression-free survival is determined programmatically from adjudicated PD, defined as the interval from the start of treatment until the first date on which recurrence, progression (per RECIST v1.1) or death due to any cause, is documented, censored at the last assessable evaluation, or at the initiation of new anticancer therapy. It is not necessary to confirm disease progression.

13.8 Overall Survival

Overall survival is defined as the time from the start of treatment to death due to any cause.

13.9 Clinical Benefit Rate

The CBR is defined as the proportion of patients who achieved overall tumor response (CR or PR) or SD for at least 24 weeks. Stable disease is measured from enrollment until the criteria for disease progression or response are met, per RECIST v1.1

14.0 Data Reporting/Protocol Deviations

14.1 Data Reporting

14.1.1 Confidentiality and Storage of Records

Electronic Data Collection will be used for this protocol. The data will be stored in encrypted, password protected, secure computers that meet all HIPAA requirements. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed. Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA, HHS, or other authorized users such as the NCI, under the guidelines established by the Federal Privacy Act and rules for the protection of human subjects.

14.1.2 Subject Consent Form

At the time of registration, the original signed and dated Informed Consent form, HIPAA research authorization form, and the California Experimental Subject's Bill of Rights (for the medical record) and three copies (for the subject, the research record, and the Coordinating Center) must be available. All Institutional, NCI, Federal, and State of California requirements will be fulfilled.

14.1.3 Data Collection Forms and Submission Schedule

All data will be collected using electronic data collection, stored as indicated in Section 12.1.1, and submitted according to the timelines indicated in **Table 16**.

Table 16: Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 10 calendar days of treatment administration
Adverse Event Report Forms	For Cycle 1 only, within 7 calendar days of AE assessment/notification; for all other cycles, within 10 calendar days of AE assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms (as applicable)	Within 10 calendar days of the assessment

Off Treatment/Off Study Forms	Within 10 calendar days of completing treatment or being taken off study for any reason
Follow up/Survival Forms	Within 14 calendar days of the protocol defined follow up visit date or call

14.1.3.1 Eligibility Checklist

The Eligibility Checklist must be completed by a protocol nurse or clinical research associate and signed by an authorized investigator prior to registering the subject. See Section 4.3 for the registration procedure.

14.2 Protocol Deviations

14.2.1 Deviation Policy

This protocol will be conducted in accordance with COH's "Clinical Research Protocol Deviation Policy" located at http://www.coh.org/dsmc/Documents/Institutional%20Deviation%20Policy.pdf. Deviations from the written protocol that could increase patient risk or alter protocol integrity require prior IRB approval of a single subject exception (SSE) request. In addition, if contractually obligated, the sponsor must also approve the deviation. IRB pre-approved SSE protocol modifications are considered an amendment to the protocol and not a deviation. The submission of a deviation report is not required.

Brief interruptions and delays may occasionally be required due to travel delays, airport closure, inclement weather, family responsibilities, security alerts, government holidays, etc. This can also extend to complications of disease or unrelated medical illnesses not related to disease progression. The PI has the discretion to deviate from the protocol when necessary so long as such deviation does not threaten patient safety or protocol scientific integrity. Examples include, but are not limited to: a) dose adjustments based on excessive patient weight; b) alteration in treatment schedule due to non-availability of the research participant for treatment; c) laboratory test results which are slightly outside the protocol requirements but at levels that do not affect participant safety. These instances are considered to be deviations from the protocol. A deviation report will be submitted to the DSMC/IRB within five days.

14.2.2 Reporting of Deviations

All deviations will be reported to the COH DSMC within five days. The DSMC will forward to report to the IRB following review.

14.2.3 Resolving Disputes

The COH Investigational Drug Service (IDS) cannot release a research agent that would cause a protocol deviation without approval by the PI. Whenever the protocol is ambiguous on a key point, the IDS should rely on the PI to clarify the issue.

In situations where there is misperception or dispute regarding a protocol deviation among the persons involved in implementing the protocol, it is the responsibility of the PI to resolve the dispute and the PI may consult with the DSMC chair (or designee) to arrive at resolution.

15.0 Statistical Considerations

The study will be an open label, single arm, phase II safety and tolerability study of neratinib (240 mg orally daily) in patients age 60 or older with HER2 positive breast cancer. As diarrhea has been seen with neratinib, we have established additional guidelines and criteria which will be used to flag an unexpected number of patients that experience grade 3 diarrhea within the 2 cycles on neratinib treatment in the presence of aggressive mandatory anti-diarrhea management which will lead to a careful data review. There will also be one interim analysis of the toxicity profile after 20 subjects have been on drug for one cycle.

15.1 Sample Size and Accrual Rate

Given a sample size of 40 subjects the widest half-width of the 95% confidence limits for the rate of grade 2 or higher toxicities will be less than or equal to 0.16. For example if we saw a toxicity rate of 0.2 (8 subjects/40) the 95% lower and upper confidence limits would be .09 and .36, respectively. With a sample size of 40, we would expect to see toxicity that has a true rate of occurrence of 0.05 in 87% of trials. We expect an accrual rate of 3 subjects every 2 months, for a total accrual rate of 18 subjects per year. With this rate, the full complement of 40 subjects will be accrued over a 30 month period. The median number of cycles for this patient population is approximately 9, so we would expect to complete this study in 42 to 48 months.

15.2 Interim Analyses and Stopping rules

15.2.1 Interim Analyses

After 20 patients have completed one full cycle of therapy, the study team will review the data, determine the rate of grade 2 and above toxicities attributed (level possibly and above) to neratinib, and assess the toxicity profile in general and specifically look at all grades of GI toxicities. We will also estimate the rates of dose reduction, holds, and hospitalization related to the neratinib. Within this interim analysis we will include a specific review the data from the participants over 75 years of age.

15.2.2 Stopping Rules (see **Table 17**)

As diarrhea has been seen with neratinib, we have established additional guidelines and criteria which will be used to flag an unexpected number of patients that experience grade 3 diarrhea within the 2 cycles on neratinib treatment in the presence of aggressive mandatory anti-diarrhea management.

The risk set to be used in the safety monitoring decision (to trigger a review of the protocol) will include all patients that have received the neratinib in the presence of aggressive mandatory anti-diarrhea management.

Every time a patient experience ≥ grade 3 diarrhea within the first 2 cycles on treatment in the presence of aggressive mandatory anti-diarrhea management we will look at the column for the total number of patients that have experienced this toxicity (X), and compare the total number of patients, N, who are in the risk set to N_X. If the total number of patients, N, is greater than N_X, the number given in the bottom row of the table below, then accrual will continue. If N is less than or equal to N_X, then the monitoring boundary will have been crossed and a careful review of the trial data will be mandated.

Table 17: Criteria for Suspending Accrual to Evaluate Safety

X: # pts who experience ≥ grade 3 diarrhea within the first 2 cycles on neratinib treatment in the presence of aggressive mandatory anti-diarrhea management.	4	5	6	7	8	9	10	11	12
Nx: safety boundary crossed if # patients in risk set (N) is less than or equal to Nx (if N ≤ Nx)	≤6	≤ 11	≤ 16	≤20	≤25	≤29	≤34	≤38	≤40

These rules were selected to ensure a low probability that the safety boundary would be crossed, indicating excessive ≥grade 3 diarrhea, if the true chance of ≥grade 3 diarrhea were less than 15% and a high probability that the boundary would be crossed if the true chance of ≥grade 3 diarrhea reached 30%. Criteria for flagging an excessive number of patients that have toxicity are based on the sequential probability ratio test with a=0.10, b=0.10, po=0.15 and pa=0.30. The table below summarizes these probabilities. The values in **Table 18** below are based on 10,000 simulations.

Table 18: Probability of Crossing the Safety Boundary (i.e. too many patients have TOX)

True Chance of Experiencing experience ≥ grade 3 diarrhea within the first 2 cycles on neratinib treatment in the presence of aggressive mandatory anti-diarrhea management.	5%	15%	30%	50%
Probability of Crossing the Safety Boundary	<0.001	0.07	0.71	>.99

15.3 Data Analysis

Tables will be created to summarize the toxicities and side effects by organ system, attribution and severity for all participants that receive at least one dose of neratinib.

Rates and associated 95% exact Clopper and Pearson binomial confidence limits will be estimated for 1) grade 2 or higher toxicities attributed to neratinib, 2) all grade GI toxicities (diarrhea, nausea and vomiting), 3) dose reductions, holds and hospitalizations, and 4) the objective response (CR+PR) and clinical benefit (CR+PR+SD) and 5) 16 week progression free survival(PFS). EFS, PFS and OS will be estimated using the product limit method of Kaplan and Meier. Descriptive statistics will be provided for drug adherence and participant demographics. Serum samples from this study will be integrated into a population PK analysis dataset to explore the effects of age on PK parameters (clearance and volume of distribution) and exposure-response relationships on efficacy and safety of neratinib. Generalized linear models and graphical methods will be used to explore factors as identified by a cancer-specific geriatric assessment and serum biomarkers that may be predictive of toxicity dose reductions, dose holds or hospitalizations. We will use generalized linear models to determine if any of these factors independently predict toxicity, response, and/or pharmacokinetic parameters of interest.

16.0 Human Subject Issues

16.1 Institutional Review Board

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

16.2 Recruitment of Subjects

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team, from the pool of patients seen by the study center with locally advanced or metastatic breast cancer. Potential subjects will be contacted by their treating physician and will be referred to the investigator/research staff of the study at their institution.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at the participating institution, provided that the investigator/research team is only reviewing records at their home institution, in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patients regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial

conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted by the treatment team, investigator, or the research staff working in conjunction with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened, and minimal PHI will be maintained as part of a screening log. For these reasons we seek a limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable). Treating physicians will be contacted regarding potentially eligible patients, and may then choose whether to offer eligible patients the opportunity to participate in the study. The goals of the study will be described and the patient will be given a copy of the informed consent to review. The interested patient will sign the consent form and retain a copy.

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Blood tests that were performed within 14 days and radiologic tests performed within 28 days for clinical indications (not exclusively to determine study eligibility) may be used for baseline values, even if the studies were done before informed consent was obtained.

16.3 Advertisements

Advertisements to include print, media (radio, television, billboards), telephone scripts, lay summary to be posted on City of Hope's public Clinical Trials On-Line^{SM} website, etc., will be reviewed and approved by the IRB prior to their use to recruit potential study subjects.

16.4 Study location and Performance Sites

This study will be performed at COH including the main campus, South Pasadena and Antelope Valley. Other sites may enroll patients onto the research protocol provided that this protocol, with site-specific changes only, is approved by each site IRB. All data analysis will be performed at City of Hope.

16.5 Confidentiality

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI). The study will record individual response to the study drugs and any side effects, and this will be linked to the subject's identity using a coded study number. The principal investigator, co-investigators, and laboratory technicians will have access to this information, but all

information will be treated confidentially. No identifiers will be used in any subsequent publication of these results.

16.6 Financial Obligations and Compensation

The study drug neratinib will be provided by the manufacturer free of charge to patients on this study. Pharmacokinetic lab draws, processing, and results will also be free of charge as a part of research. Routine standard of care clinic visits, laboratory tests, and tumor imaging will be billed to the patient and/or the patient's insurance. Cardiac imaging will be provided free of charge. Medication and/or treatment needed for side effects of study drug will be billed to the patient and/or the patient's insurance.

If there is a serious medical complication of the research, treatment will be available at City of Hope, but there will be no compensation to the subject for this injury.

16.7 Informed Consent Processes

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Research subjects will be afforded sufficient time to consider whether or not to participate in the research.

Should sufficient doubt be raised regarding the adequacy of comprehension, further clarifications will be made and the questionnaire repeated until a satisfactory result is obtained. Prospective research subjects who cannot adequately comprehend the fundamental aspects of the research study with a reasonable amount of discussion, education and proctoring will be ineligible for enrollment. For those subjects who do comprehend the fundamental aspects of the study, consent will be obtained and documented, followed by eligibility testing. The research team will review the results of eligibility testing and determine if the subject is a candidate for study enrollment.

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APPENDIX A: ECOG Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Criteria**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Karnofsky Performance Status Criteria

Karnofsky Performance Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
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.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead

APPENDIX C: Multicenter Guidelines

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with sponsoring organization. The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to the FDA and Puma Biotechnology Inc. (Puma) are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Data Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Data Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- The Data Coordinating Center is responsible for central patient registration of patients from participating institutions. The Data Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Data Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair that has been received by the participating institutions.
- The Data Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to the FDA and Puma with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to Puma and the FDA. The Data Coordinating Center will submit AE reports to the Protocol Chair for timely review.

- Routine monitoring of data quality will take place for all data received from participating institutions. The participating institution will be asked to provide the Data Coordinating Center source documentation pertaining to the data collected. This information should be de-identified by the participating institution prior to faxing to the Data Coordinating Center.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are sent from participating sites to the Data Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the study sponsor chooses to have an audit at the Data Coordinating Center, then the Data Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

The protocol must include the following minimum information:

- The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
- The Data Coordinating Center must be designated on the title page.
- Central registration of patients is required. The procedures for registration must be stated in the protocol.
- Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Data Coordinating Center should be stated.
- Describe how AEs will be reported from the participating institutions through the Data Coordinating Center.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order neratinib directly from Puma Biotechnology Inc.

APPENDIX D: Substrates and Inhibitors of P-glycoprotein (P-gp) [a]

P-glycoprotein Substrates		
Amiodarone (eg, Cordarone)	Fluphenazine (eg, Prolixin)	Progesterone (eg, Prometrium)
Chlorpromazine (eg, Thorazine)	Hydrocortisone (eg, Cortef)	Promethazine (eg, Phenergan)
Clarithromycin (eg, Biaxin)	Indinavir (Crixivan	Quinidine
Cyclosporine (eg, Neoral)	Itraconazole (eg, Sporanox)	Reserpine
Dactinomycin (Cosmegen)	Ketoconazole (eg, Nizoral)	Ritonavir (Norvir)
Daunorubicin (eg, Cerubidine)	Lidocaine (eg, Xylocaine)	Saquinavir (eg, Fortovase)
Dexamethasone (eg, Decadron)	Loperamide (eg, Imodium)	Sirolimus (Rapamune)
Digoxin (eg, Lanoxin)	Lovastatin (eg, Mevacor)	Tacrolimus (Prograf)
Diltiazem (eg, Cardizem)	Mifepristone (Mifeprex)	Tamoxifen (eg, Nolvadex)
Doxorubicin (eg, Adriamycin)	Mitoxantrone (Novantrone)	Teniposide (Vumon)
Erythromycin (eg, Ery-Tab)	Nelfinavir (Viracept)	Testosterone Delatestryl)
Estradiol (eg, Estrace)	Nicardapine (eg, Cardene)	Trifluoperazine
Etoposide (eg, Vepesid)	Nifedipine (eg, Procardia)	Verapamil (eg, Calan)
Felodipine (Plendil)	Ondansetron (Zofran)	Vinblastine (eg, Velban)
Fexofenadine (Allegra)	Paclitaxel (eg, Taxol)	Vincristine (eg, Vincasar PFS)
P-glycoprotein Inhibitors		
Amiodarone (eg, Cordarone)	Indinavir (Crixivan)	Quinidine
Atorvastatin (Lipitor)	Itraconazole (eg, Sporanox)	Reserpine
Chlorpromazine (eg, Thorazine)	Ketoconazole (eg, Nizoral)	Ritonavir (Norvir)
Clarithromycin (eg, Biaxin)	Lidocaine (eg, Xylocaine)	Saquinavir (eg, Fortovase)
Cyclosporine (eg, Neoral)	Mifepristone (Mifeprex)	Tacrolimus (Prograf)
Diltiazem (eg, Cardizem)	Nelfinavir (Viracept)	Tamoxifen (eg, Nolvadex)
Erythromycin (eg, Ery-Tab)	Nicardipine (eg, Cardene)	Testosterone (Delatestryl)
Felodipine (Plendil)	Nifedipine (eg, Procardia)	Trifluoperazine
Fluphenazine (eg, Prolixin)	Progesterone (eg, Prometrium)	Verapamil (eg, Calan
Hydrocortisone (eg, Cortef)	Propranolol (eg, Inderal)	

a. This list is not all inclusive and may change.

APPENDIX E: Drugs Associated with Risk of QT/QTc Prolongation Leading to Torsade de Pointes[c]

Drugs Reported to Prolong QT Interval		
Analgesics		
Celecoxib (Celebrex)	Methadone (e.g., Dolophine, Methadose)	
Anesthetic agents		
Enflurane (e.g., Ethrane)	Halothane	
Isoflurane (e.g., Forane)		
Antiarrhythmic agents		
Class IA	Class III	
Disopyramide (e.g., Norpace)*	Amiodarone (e.g., Cordarone)*b	
Procainamide (e.g., Procanbid)*	Bretylium*	
Quinidine*	Dofetilide (Tikosyn)*b	
Class IC	Ibutilide (Corvert)*b	
Flecainide (e.g., Tambocor)*a	Sotalol (e.g., Betapace)*b	
Propafenone (e.g., Rythmol)*b		
Anticonvulsants		
Felbamate (Felbatol)*	Fosphenytoin (Cerebyx)	
Antiemetics		
Dolasetron (Anzemet)b	Droperidol (e.g., Inapsine)*b	Ondansetron (Zofran)
Antihistamines		
Desloratadine (Clarinex) (overdose)b	Fexofenadine (Allegra)	
Diphenhydramine (e.g., Benadryl)	Hydroxyzine (Atarax)	
Anti-infectives		
Amantadine (e.g., Symmetrel)*	Macrolides and related antibiotics	
Antimalarials	Azithromycin (e.g., Zithromax)	
Mefloquine (e.g., Lariam)b	Clarithromycin (e.g., Biaxin)*b	
Quinine*	Erythromycin (e.g., Ery-Tab, EES)*b	
Antivirals	Telithromycin (Ketek)b	
Efavirenz (Sustiva)*	Troleandomycin	
Azole antifungal agents	Pentamidine (e.g., Pentam 300, Nebupent)*	
Fluconazole (e.g., Diflucan)*b	Quinolones	
Itraconazole (e.g., Sporanox)	Gatifloxacin (e.g., Tequin)*b	
Ketoconazole (e.g., Nizoral)	Levofloxacin (e.g., Levaquin)*a.b	
Voriconazole (Vfend)b	Moxifloxacin (e.g., Avelox)b	
Chloroquine (e.g., Aralen)*	Ofloxacin (e.g., Floxin)*b	
Clindamycin (e.g., Cleocin)	Sparfloxacin (Zagam)b	

Foscarnet (Foscavir)	Trimethoprim/sulfamethoxazole (e.g., Bactrim)*	
Antineoplastics		
Arsenic trioxide (Trixenox)*b	Doxorubicin (e.g., Adriamycin)	Tamoxifen (e.g., Nolvadex)
Bronchodilators		
Albuterol (e.g., Proventil)b	Salmeterol (Serevent) b	
Formoterol (Foradil) b	Terbutaline (e.g., Brethine) b	
Isoproterenol (e.g., Isuprel)		
Calcium channel blockers		
Isradipine (DynaCirc)	Nicardipine (e.g., Cardene)	
Contrast media		
Ionic contrast media*	Non-ionic contrast media: Iohexol (Omnipaque)	
Corticosteroids		
Prednisolone (e.g., Prelone)	Prednisone (e.g., Deltasone)*	
Diuretics		
Furosemide (e.g., Lasix)	Indapamide (e.g., Lozol)	
Gastrointestinal agents		
Cisapride (Propulsid)*b,c	Famotidine (e.g., Pepcid)*	
Immunosuppressants		
Tacrolimus (Protopic)* (postmarketing)b		
Miscellaneous		
Levomethadyl	Papaverine (e.g., Pavaden three times daily [TID])*	
Moexipril/Hydrochlorothiazide (Uniretic)	Probucol (Lorelco)*c	
Octreotide (Sandostatin)b	Vasopressin (e.g., Pitressin)*	
Oxytocin (e.g., Pitocin; intravenous bolus)		
Psychotropics		
Droperidol (e.g., Inapsine)*	Primozide (Orap)*b,d	Trazodone (e.g., Desyrel)
Haloperidol (e.g., Haldol)*	Quetiapine (Seroquel)b	Tricyclic antidepressants
Lithium (e.g., Eskalith)*	Risperidone (Risperdal) (overdose)b	Amitriptyline*
Maprotiline*	Serotonin Reuptake Inhibitors (SRIs)	Clomipramine (e.g., Anafranil)
Phenothiazines	Citalopram (e.g., Celexa)*	Desipramine (e.g., Norpramin)*
Chrlorpromazine (e.g., Thorazine)*	Fluoxetine (e.g., Prozac)*a	Doxepin (e.g., Sinequan)*
Fluphenazine (e.g., Prolixin)*	Paroxetine (e.g., Paxil)*	Imipramine (e.g., Tofranil)*
Perphenazine	Sertraline (Zoloft)* (postmarketing)a,b	Nortriptyline (e.g., Pamelor)

Thioridazine (Mellaril)* b	Venlafaxine (Effexor) b	
Trifluopherazine		
Serotonin 5-HT agonists		
Naratriptan (Amerge)	Sumatriptan (Imitrex) b	Zolmitriptan (Zomig) b
Skeletal muscle relaxants		
Tizanidine (e.g., Zanaflex) (animals) b		

*Drug for which Torsades de Pointes has also been reported
a, Association unclear
b, QT, QTc and/or Torsades de Pointes association listed in FDA approved product labeling

Source: Tatro, DS. Drug-induced Prolongation of the QT Interval and Torsades de Pointes. Drug Interaction Facts. The Authority on Drug Interactions. Wolters Kluwer Health 2012

c. This list is not all inclusive and may change.

APPENDIX F: Inhibitor and Inducers of the Cytochrome A P450 Isoenzymes[a]

CYP3A4 Inhibitors		
Amprenavir	Grapefruit juice	Paroxetine
Anastrozole	Indinavir	Propranolol
Cimetidine	Itraconazole	Quinidine
Clarithromycin	Ketoconazole	Quinine
Clotrimazole	Mibefradil	Ranitidine
Danazol	Miconazole	Ritonavir
Delavirdine	Mirtazapine (weak)	Saquinavir
Diethyldithiocarbamate	Nefazodone	Sertraline
Diltiazem	Nelfinavir	Sildenafil (weak)
Erythromycin	Nevirapine	Troglitazone
Fluconazole	Norfloxacin	Troleandomycin
Fluoxetine	Norfluoxetine	Zafirlukast
Fluvoxamine		
CYP3A4 Inducers		
Carbamazepine	Macrolide antibiotics	Rifabutin
Efavirenz	Phenobarbital	Rifampin
Glucocorticoids:	Phenylbutazone	Rifapentine
Dexamethasone	Phenytoin	St. John's Wort
Prednisone	Primidone	Sulfinpyrazone
CyP3A5-7 Inducers		
Phenobarbital	Primidone	Rifampin
Phenytoin		

Source: Tatro DS, Drug Interaction Facts: The Authority on Drug Interactions. Wolters Kluwer Health 2012.

a This list is not all inclusive and may change.

APPENDIX G: Eligibility Checklist

Inclusion Criteria	Yes	No
Is this patient age 60 or older?		
Is this patient's ECOG performance 0-2?		
Does the patient have a life expectancy of >12 weeks?		
Does the patient have histologically or cytologically proven metastatic breast cancer?		
Does this patient have documented HER2 positive disease per ASCO CAP guidelines?	IHC:	
	FISH:	
Does this patient have stage IV Her2/Neu positive breast cancer and failed previous anti-HER2 targeted therapies? There is no limitation on the number of prior lines of systemic therapy or HER2-targeted therapies.		
If HER2 negative, does the tumor have documented HER2 gene mutations through CLIA certified laboratory test? (Missense substitutions (G309A, G309E, S310F, S310Y, S653C, V659E, R678Q, V697L, T733I, L755S, L755P, E757A, D769H, D769Y, D769N, G776V, G776C, V777L, L841V, V842I, R849W, L869R, R896C); Insertions/deletions (A775_G776insYVMA aka Y772_A755dup, G776VinsC, G776AinsVGC,G776 insertions, G778_S779insCPG, P780_781insGSP aka G778_P780dup, L755_T759del).		
Does the patient have adequate organ and bone marrow functions within 4 wk of pre-registration: o Hemoglobin: ⩾ 9g/dL (after transfusion, if necessary) o Total bilirubin: within normal institutional limits o AST (SGOT)/ALT (SGPT): ⩽ 2.5 X institutional upper limit of normal o Creatinine clearance ≥ 30 mL/minas calculated by Cockroft-Gault formula		

Does the patient have baseline LVEF ≥ 50% as evaluated by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)?		
Have all Grade ≥2 toxicities other than alopecia from prior therapy been resolved?		
Has the patient completed radiation therapy with adequate recovery of bone marrow and organ functions?		
Does the patient have stable or treated brain metastases? Asymptomatic patients with metastatic brain disease who have been on a stable dose of corticosteroids for treatment of brain metastases for at least 14 days are eligible to participate in the study.		
Has the patient been provided written, informed consent to participate in the study and follow the study procedures?		
Exclusion Criteria:	No	Yes
Has the patient previously been treated with neratinib?		
Is the patient currently using other investigational agents, chemotherapy, or hormone therapy? Prior chemotherapy, hormonal therapy, targeted therapy, and investigational agents are allowed but all toxicities grade ≥2 must have resolved by the time of study commencement (except alopecia).		
Has the patient had any major surgery ≤ 28 days prior to the initiation of investigational products, or received anti-cancer therapy (including chemotherapy, biological therapy, hormonal therapy, investigational agents, or other anti-cancer therapy) administered ≤ 14 days prior to initiation of investigational products?		
Has the patient had active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2, including individuals who currently use digitalis specifically for congestive heart failure), unstable angina, myocardial infarction within 12 month of enrollment or ventricular arrhythmia?		
Is the patient concurrently using digoxin due to cardiac disease?		

Does the patient have QTc interval ≥450 milliseconds (men) and ≥ 470 milliseconds (women) within 2 weeks of registration or known history of QTc prolongation or Torsades de Pointes?		
Is the patient unable to take oral medication?		
Does the patient have any known hypersensitivity to any component of the investigational product?		
Does the patient have other malignancy within the past 3 years with the exception of: a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) cervix or vulva carcinoma in situ; c) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder, or benign tumors of the adrenal or pancreas?		
Does the patient have significant chronic gastrointestinal disorder with diarrhea as a major symptom (e.g., Crohn's disease, malabsorption, or Grade ≥2 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE v.4.0] diarrhea of any etiology at baseline)?		
Does the patient have known clinically active infection with hepatitis B or hepatitis C virus?		
Does the patient have evidence of significant medical illness, abnormal laboratory finding or psychiatric illness/social situations that would, in the Investigator's judgment, makes the patient inappropriate for this study?		

APPENDIX H: Self Geriatric Assessment Measure – Patient Questionnaire

Responsible person name (*Physician, Nurse, or CRA*) _____
Assessment Period (as applicable to this study):
☐ Timepoint 1 (Baseline); ☐ Timepoint 2 (At cycle #4); ☐ Timepoint 3 (End of study)

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

A. BACKGROUND INFORMATION

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

☐ 8th or less
☐ 9-11th grade
☐ High school graduate/GED
☐ Associate degree/some college
☐ Vocational/technical school
☐ Bachelor's degree
☐ Advanced degree
☐ I prefer not to answer

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

☐ Married
☐ Domestic partnership
☐ Widowed
☐ Divorced
☐ Separated
☐ Never married
☐ I prefer not to answer

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

☐ Spouse / partner
☐ Girlfriend / boyfriend
☐ Children aged 18 years or younger
☐ Children aged 19 years or older
☐ Parent(s)/ parent(s)-in-law
☐ Live alone
☐ Other specify _____
☐ Other relative specify

_____

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

☐ Employed 32 hours or more per week ☐ Unemployed

☐ Employed less than 32 hours per week ☐ Retired

☐ Homemaker ☐ Full-time student

☐ Disabled ☐ Part-time student

☐ On medical leave ☐ Other specify _____

5. How old are you? _____ years old

6. What is your race? (Mark one with an X)

☐ White ☐ Asian

☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander

☐ Native Indian or Alaskan Native ☐ Unknown

7. What is your ethnicity? (Mark one with an X)

☐ Hispanic or Latino

☐ Non-Hispanic

☐ Unknown

B. DAILY ACTIVITIES*

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

1. Can you use the telephone…

☐ without help, including looking up and dialing;

☐ with some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the phone number or dialing); or

☐ are you completely unable to use the telephone?

2. Can you get to places out of walking distance…
   - ☐ without help (can travel alone on busses, taxis, or drive your own car);
   - ☐ with some help (need someone to help you or go with you when traveling) ; or
   - ☐ are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?

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

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

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

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

7. Can you handle your own money…
   - ☐ without help (write checks, pay bills, etc.);

☐ with some help (manage day-to-day buying but need help with managing your checkbook and paying your bills); or

☐ are you completely unable to handle money?

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

C. PHYSICAL ACTIVITIES*

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

Activities	Limited a lot	Limited a little	Not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
c. Lifting or carrying groceries	☐	☐	☐
d. Climbing several flights of stairs	☐	☐	☐
e. Climbing one flight of stairs	☐	☐	☐
f. Bending, kneeling, or stooping	☐	☐	☐
g. Walking more than a mile	☐	☐	☐
h. Walking several blocks	☐	☐	☐
i. Walking one block	☐	☐	☐
j. Bathing or dressing yourself	☐	☐	☐

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

D. CURRENT HEALTH RATING*

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

☐ Normal, no complaints, no symptoms of disease

☐ Able to carry on normal activity, minor symptoms of disease

☐ Normal activity with effort, some symptoms of disease

☐ Care for self, unable to carry on normal activity or do active work

☐ Require occasional assistance but able to care for most of personal needs

☐ Require considerable assistance for personal care

☐ Disabled, require special care and assistance

☐ Severely disabled, require continuous nursing care

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

E. FALLS

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

F. YOUR MEDICATIONS

Are your taking medications?

☐ Yes ☐ No

How many prescribed medications are you taking? ___ medications

How many over-the-counter medications are you taking? ___ medications

How many herbs and vitamins are you taking? ___ herbs and vitamins

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G. YOUR HEALTH

1. Your General Health*

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

Illness	No	Yes		If you have this illness: How much does it interfere with your activities? Not at all	A little	A great deal
a. Other cancers or leukemia	☐	☐	→	☐	☐	☐
b. Arthritis or rheumatism	☐	☐	→	☐	☐	☐
c. Glaucoma	☐	☐	→	☐	☐	☐
d. Emphysema or chronic bronchitis	☐	☐	→	☐	☐	☐
e. High blood pressure	☐	☐	→	☐	☐	☐
f. Heart trouble	☐	☐	→	☐	☐	☐
g. Circulation trouble in arms or legs	☐	☐	→	☐	☐	☐
h. Diabetes	☐	☐	→	☐	☐	☐
i. Stomach or intestinal disorders	☐	☐	→	☐	☐	☐
j. Osteoporosis	☐	☐	→	☐	☐	☐
k. Liver disease	☐	☐	→	☐	☐	☐
l. Kidney disease	☐	☐	→	☐	☐	☐
m. Stroke	☐	☐	→	☐	☐	☐
n. Depression	☐	☐	→	☐	☐	☐

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

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

☐ Excellent

☐ Good

☐ Fair

☐ Poor

☐ Totally blind

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

   ☐ Excellent

   ☐ Good

   ☐ Fair

   ☐ Poor

   ☐ Totally deaf

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

   ☐ No

   ☐ Yes *(If yes),* specify _____

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

   ☐ Not at all ☐ Somewhat ☐ A great deal

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

H. NUTRITIONAL STATUS

1. Have you lost weight involuntarily over the past 6 months?

   ☐ No

   ☐ Yes

   If yes, how much?

   _____ pounds

2. What is your weight now?

   _____ pounds

3. What was your weight 6 months ago?

   _____ pounds

I. HEALTH QUESTIONNAIRE*

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

How much of the time during the past month:	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
1. has your daily life been full of things that were interesting to you?	☐	☐	☐	☐	☐	☐
2. did you feel depressed?	☐	☐	☐	☐	☐	☐
3. have you felt loved and wanted?	☐	☐	☐	☐	☐	☐
4. have you been a very nervous person?	☐	☐	☐	☐	☐	☐
5. have you been in firm control of your behavior, thoughts, emotions, feelings?	☐	☐	☐	☐	☐	☐
6. have you felt tense or high-strung?	☐	☐	☐	☐	☐	☐
7. have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
8. have you felt emotionally stable?	☐	☐	☐	☐	☐	☐
9. have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
10. have you felt restless, fidgety, or impatient?	☐	☐	☐	☐	☐	☐
11. have you been moody, or brooded about things?	☐	☐	☐	☐	☐	☐
12. have you felt cheerful, light-hearted?	☐	☐	☐	☐	☐	☐
13. have you been in low or very low spirits?	☐	☐	☐	☐	☐	☐
14. were you a happy person?	☐	☐	☐	☐	☐	☐
15. did you feel you had nothing to look forward to?	☐	☐	☐	☐	☐	☐

16. have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
17. have you been anxious or worried?	☐	☐	☐	☐	☐	☐

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

J. SOCIAL ACTIVITIES*

1. During the past 4 weeks, how much time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? *(Mark one with an X.)*

   ☐ All of the time
   ☐ Most of the time
   ☐ Some of the time
   ☐ A little of the time
   ☐ None of the time

2. Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition? *(Mark one with an X.)*

   ☐ Much less socially active than before
   ☐ Somewhat less socially active than before
   ☐ About as socially active as before
   ☐ Somewhat more socially active as before
   ☐ Much more socially active than before

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

☐ Much more limited than others

☐ Somewhat more limited than others

☐ About the same as others

☐ Somewhat less limited than others

☐ Much less limited than others

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

K. SOCIAL SUPPORT*

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

	None of the Time	A Little of the Time	Some of the Time	Most of the Time	All of the Time
1. Someone to help you if you were confined to bed.	☐	☐	☐	☐	☐
2. Someone you can count on to listen to you when you need to talk.	☐	☐	☐	☐	☐
3. Someone to give you good advice about a crisis.	☐	☐	☐	☐	☐
4. Someone to take you to the doctor if you needed it.	☐	☐	☐	☐	☐
5. Someone to give you information to help you understand a situation.	☐	☐	☐	☐	☐
6. Someone to confide in or talk to about yourself or your problem.	☐	☐	☐	☐	☐
7. Someone to prepare your meals if you were unable to do it yourself.	☐	☐	☐	☐	☐
8. Someone whose advice you really want.	☐	☐	☐	☐	☐
9. Someone to help you with daily chores if you were sick.	☐	☐	☐	☐	☐
10. Someone to share your most private worries	☐	☐	☐	☐	☐

and fears with.					
11. Someone to turn to for suggestions about how to deal with a personal problem.	☐	☐	☐	☐	☐
12. Someone who understands your problems.	☐	☐	☐	☐	☐

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

L. SPIRITUALITY/RELIGION*

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

1. How often do you attend church, synagogue, or other religious meetings? *(Mark one with an X.)*
   - ☐ More than once per week
   - ☐ Once a week
   - ☐ A few times a month
   - ☐ A few times a year
   - ☐ Once a year or less
   - ☐ Never

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

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

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

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

5. I tried hard to carry my religion over into all other dealings in my life. *(Mark one with an X.)*
   - ☐ Definitely true of me
   - ☐ Tends to be true
   - ☐ Unsure
   - ☐ Tends *not* to be true
   - ☐ Definitely *not* true

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

M. YOUR FEELINGS*

1. Do you often feel sad or depressed? *(Mark one with an X.)*

   ☐ No ☐ Yes

2. How would you describe your level of anxiety, on the average? Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

0 1 2 3 4 5 6 7 8 9 10

No anxiety can be — Anxiety as bad as it

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

N. FACT-B

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4

GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my	0	1	2	3	4

	illness					
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4

GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get	0	1	2	3	4
	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4

GF7	I am content with the quality of my life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

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

B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

O. QUESTIONS CONCERNING THE QUESTIONNAIRE

1. Were there any questions difficult to understand? ☐ No ☐ Yes

   (If yes), which questions were they?

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

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

   ☐ Just right

   ☐ Too long → How long would you have liked the questionnaire to be? __ __ minutes

   Which items would you remove?

3. Did you find any of the questions upsetting? ☐ No ☐ Yes

   (If yes), which questions were they?

Could you tell me why they were upsetting?

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

Thank you for your participation.

APPENDIX I: Geriatric Assessment Healthcare Professional Questionnaire

I. This form completed by: (Mark all that apply with an X.) Assessment Period (as applicable to this study)

□ Physician □ Nurse □ CRA □ Pre-treatment □ Cycle #4 □ End of Treatment

□ **Mark box with an "X", if form was not completed at specified timepoint and specify reason:**

(Mark one with an X.) □ Patient refused □ Patient withdrew consent □ Not done

□ Other, specify _____

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

II. Karnofsky Performance Status: _____%

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

DEFINITION	%	CRITERIA
Able to carry on normal activity and able to work. No special care is needed.	100	Normal: no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal Activity with effort; some signs or symptoms of disease.
Unable to work. Able to live at home, and for most personal needs. A varying amount of assistance is needed	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated although death not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly
	0	Dead.

* Physician KPS – Karnofsky, D.A. and Burchenal, J.H., 1949

Geriatric Assessment Healthcare Professional Questionnaire

III. Timed "Up and Go"*

INSTRUCTIONS: The timed "Up and Go" measures, in seconds, the time it takes for an individual to stand up from a standard arm chair (approximate seat height of 46 cm [approximately 1.5 ft]), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down again. The subject wears his/her regular footwear and uses their customary walking aid (none, cane, walker, etc.) No physical assistance is given.

The subject starts with his back against the chair, his arm resting on the chair's arm, and his walking aid in hand. He is instructed that on the word "go", he is to get up and walk at a comfortable and safe pace to a line on the floor three meters (approximately ten feet) away, turn, and return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a wrist watch with a second hand or a stop-watch can be used to time the performance.

Time to perform "Up and Go" seconds :_____

IV. COGNITION : Orientation-Memory-Concentration Test

Errors	**Patient's Final Score**	**Maximum Response Weight**	**Score**
1. What year is it now? ☐ x [without looking at a calendar]	☐☐☐☐ 4	1 =	☐☐
2. What month is it now? ☐ x [without looking at a calendar]	☐☐ 3	1 =	☐☐

Memory Phrase

Repeat this phrase after me: 'John Brown, 42 Market Street, Chicago'.

3. About what time is it ☐ x [within 1 hour – without looking at your watch]	☐☐:☐☐ 3	1 =	☐☐
4. Count backwards from ☐ 20 to 1.		2 x	2 = ☐☐

5.	Say the months in reverse order. ☐	2 x	2 =	☐☐
6.	Repeat the memory phrase ☐	5 x	2 =	☐☐
	Score:		**Total** ☐☐	

Scoring: For items 1 to 3, the response is either correct (score 0) or incorrect (score 1). For items 4 to 6, subtract one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all scores in "Final Score" column. **Total score of 11 or greater indicates cognitive impairment; please notify MD and assist patient in completing questionnaires. Maximum score = 28**

V. Nutrition

a) What is the patient's height? _____

b) What is the patient's current weight? _____

c) What is the patient's weight approximately 6 months ago? _____

d) Calculated Body Mass Index: _____

Body Mass Index=Weight/(Height)^2

e) Percent Unintentional Weight Loss: _____

% unintentional weight loss =

(unintentional weight lost in last 6 months/baseline body weight) x 100

VI. Labs: (performed within 4 weeks of this assessment)

a) Creatinine:_____

b) Hemoglobin:_____

c) Albumin:_____

d) Liver Function Tests: Normal or Not normal_____

e) WBC: _____

f) CA125 (Gynecological patients ONLY):_____

g) Blood Urea Nitrogen: _____

VII. Scoring

a) Did the patient score ≥ 11 on the Blessed Orientation-Memory-Concentration Test (see previous page)?

☐ No

☐ Yes (if yes, notify the patient's treating physician)

VIII. Was the patient able to complete "Geriatric Assessment – Patient Questionnaire" on his/her own?

□Yes □No

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

□ Not literate (does not read or write)

□ Visual problem

□ Fatigue

□ Questions too difficult (above the patient's reading ability)

□ Other: specify_____

IX. Time to complete

a) Appendix H (Questionnaires to be completed by the study participant)

Start Time:_____

End Time: _____

b) Appendix I (Data to be gathered by the healthcare team)

Start Time:_____

End Time: _____

Total time to complete Appendix H and I: _____

Name of person completing this document: _____

Signature: _____

Date: _____

APPENDIX J: SAE/UP Reporting Coversheet

NOTIFICATION OF UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT

For Use by Participating Institutions Only

THIS FORM ALONG WITH A COPY OF THE MEDWATCH 3500A FORM MUST BE **EMAILED** TO DCC@COH.ORG WITHIN 24 HOURS OF KNOWLEDGE OF ONSET OF SERIOUS ADVERSE EVENT OR UNANCTICIPATED PROBLEM

COH IRB # (insert once IRB number known) - Participating Site IRB # _____

Staff Submitting Form:	Date:
Phone No.:	Email:

Reporting Investigator:	
Event:	
Participant ID:	Institution:
Date Event Met Reporting Criteria (as defined in protocol):	

Type of Report: ☐ Initial ☐ Follow-up

CTCAE Grade: ☐ G1/mild ☐ G2/moderate ☐ G3/severe ☐ G4/life threatening ☐ G5

Attribution to Neratinib: ☐ Unrelated ☐ Unlikely ☐ Possible ☐ Probable ☐ Definite

Meets Definition of Serious AE: ☐ Serious ☐ Non-serious

Meets Definition of Unanticipated Problem: ☐ UP ☐ Not a UP

Has the event been reported to the participating institution's IRB? __ No __ Yes

Date: __ __ / __ __ / __ __ (If yes, please attach report to this submission)

APPENDIX K: Patient Instructions For the Management of Diarrhea

Please review these instructions with your study doctor/team. Once all of your questions are answered, sign at the bottom and 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. **Use of anti-diarrheal medication is required for all enrolled subjects to help reduce or prevent diarrhea.** 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 nurse/team will call you 1 day, 2 days and 3 days 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 4 or more stools per day over usual, call your study nurse /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, call your study nurse/team immediately. If you are unable to reach assistance, please seek medical attention immediately.

Please record the number of stools and any anti-diarrheal medication taken during all Cycles of the study 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 initially take 2 tablets/capsules (4 mg) with the first dose of neratinib
- Thereafter, I will take 2 tablet/capsule (4 mg) three times a day for the next two weeks; 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 two weeks, I will take 2 tablet (4 mg) twice a day onwards through the first 1cycle of therapy (28days) from the start of neratinib regardless of whether I have diarrhea or not.
- If I continue to have diarrhea while taking loperamide, I should contact my study doctor/team for additional anti-diarrheal medication and consult.
- If I have diarrhea with increase of up to 6 stools per day over usual any time after completing the two cycles of therapy 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). _____

1.2.1 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, and I cannot reach my study doctor/team, I will stop taking the study medication and wait for further instructions from my study doctor/team.

My signature below indicates I have reviewed this information and have received the following medications:

□ Neratinib Tablets

□ Loperamide

_____

Study participant name Study participant Signature and Date

_____

Investigator delegate name Investigator delegate Signature and Date

OR

_____

Investigator name Investigator Signature and Date

APPENDIX L: Optimal Management of Diarrhea Checklist

This checklist must be completed for each patient by study team (invesetigator or study nurse) during the Day 1 visit <u>before</u> the patient leaves the site with study medication.

Patient Number: |_____|_____|_____|_____|_____|

Day 1 Visit Date: |___|___| / |___|___|___| / |___|___|

☐ I have communicated the risk and the timing of diarrhea occurrence to my patient while discussing the informed consent form and patient diarrhea instruction sheet.

☐ I have ensured that my patient takes home loperamide along with study medication.

☐ I have instructed my patient to take loperamide concomitantly with the first dose of neratinib and to take the prophylactic dose of loperamide 4mg three times a day for the next 14 days to minimize the occurrence and severity of diarrhea. Thereafter, continue to take loperamide 4mg twice a day as indicated in the protocol for first cycle (28 days).

☐ I have reviewed with my patient dietetic measures (e.g., hydration, low lactose, low fat diet enriched with bananas, rice, applesauce and toast) recommended in case he/she experiences loose stools or diarrhea.

☐ I have instructed my patient to record the number of daily stools, the occurrence of diarrhea and any anti-diarrheal treatment along with the daily dose of study medication in his/her diary daily for all cycles of study medication.

☐ I have informed my patient that he/she will receive a call at 1 day, 2 days and 3 days after first dose of study medication to assess his/her tolerance to the study medication and to document the date the first dose of study medication was taken.

☐ I will follow-up with my patient on severe diarrhea and other adverse events until resolution.

☐ I checked with my patient that he/she can be reached at _____.

☐ My patient has received my number and knows to call me as soon as he/she experiences loose stool or diarrhea (COH medical oncology call center: 626-471-9200).

Study CRA or Study Nurse's Name and Signature:

_____

_____

Loperamide is the recommended standard therapy for diarrhea in this study. Additional treatment may be required. Refer to the protocol for other therapy and literature.

APPENDIX M: Patient Diary

Date dd/mm/yy	Name of Drug	Time Taken	Dose Taken	# of Tablets per Day	# of Stools per Day	Comments on missed or reduced doses for Study Medication(s), any additional anti-diarrheal medication, and any symptoms (i.e. Diarrhea, Vomiting, Pain)
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					

Date dd/mm /yy	Name of Drug	Time Taken	Dose Taken	# of Tablets per Day	# of Stools per Day	Comments on missed or reduced doses for Study Medication(s), any additional anti-diarrheal medication, and any symptoms (i.e. Diarrhea, Vomiting, Pain)
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					
	Neratinib					
	Loperamide					

Patient Diary
Patient Number: I__I__I__I__I__I__I__I__I__I__I

Record from: _____ to: _____

Date of your next visit: _____

EMERGENCY CONTACT:

_____

Call your study team immediately if you are experiencing any new symptoms (diarrhea, vomiting, etc.).

TAKE TABLETS AS PRESCRIBED BY YOUR STUDY DOCTOR. PLEASE BRING ORIGINAL STUDY MEDICATION BOTTLES WITH YOU TO EACH STUDY VISIT

Please complete the diary every day and bring it with you to the next scheduled visit as instructed.

COMPLETION GUIDELINES

1. Enter the study drug that you are taking each day under the column "Name of Drug" and complete corresponding dose and # of tablets taken.

2. Make sure to enter the amount of loperamide you are taking as well (see example on table below).

3. If you experience diarrhea, enter # of stools per day.

Date dd/mm/yy	Name of Drug	Time Taken	Dose Taken	# of Tablets per Day	# of Stools per Day	Comments on missed or reduced doses for Study Medication(s), any additional anti-diarrheal medication, and any symptoms (i.e. Diarrhea, Vomiting, Pain)
05/Sep/12 (Day 1)	*Neratinib*		*240 mg*	*6*		
05/Sep/12	*Loperamide*		*4 mg*	*2*	*0*	
06/Sep/12	*Neratinib*		*240 mg*	*6*	*3*	*(+) diarrhea*

Appendix N: Registration Coversheet

COH IRB (Insert Please): PHASE II STUDY OF NERATINIB IN PATIENTS 60 AND OLDER WITH HER2 POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER

For use by participating instiution's staff only (not COH)

Data Coordinating Center: City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: 626-256-4673 x 83968
Email: DCC@coh.org (use #secure# in subject line)

Participating Site's CRA/Study Coordinator: _____

Contact Number: _____

<table>
<tr><td colspan="2">Patient's Initials (F M L):</td><td>Institution:</td></tr>
<tr><td colspan="2">Medical Record No: N/A</td><td>Investigator/Treating Physician:</td></tr>
<tr><td colspan="2">Patient's DOB:</td><td>IRB approval valid until (date):</td></tr>
<tr><td colspan="2">Sex: _____Male _____Female</td><td>Date Informed Consent Signed:</td></tr>
<tr><td>Race:
___ Black
___ Caucasian
___ Asian
___ American Indian
___ Native Hawaiian/Pacific Islander
___ Other _____</td><td>Ethnicity:
___ Hispanic

___ Non-Hispanic

___ Other
_____</td><td>Projected start date of treatment:

Method of payment: _____
Codes:
01 Private
02 Medicare
03 Medicare & private ins.
04 Medicaid
05 Medicaid & Medicare
06 Military or Veterans Adm. sponsored
07 Self-pay (no insurance)
08 No means of payment (no insurance)
09 Unknown</td></tr>
</table>

Appendix O: Stool Collection Procedure

STOOL COLLECTION KIT GENERAL INSTRUCTIONS

As a part of your participation in the current study, we have some specific instructions related to collection of stool. Please abide by these instructions, as they are essential for the proper conduct of the study.

You are being asked to collect samples at the following times:

- 7 days prior to start of neratinib
- C1Day 15 (+/- 3 days), C2Day1 (+/- 3 days), C2Day15 (+/-3 days), C3Day1 (+/- 3 days).

If you have any questions about sample collection, please call this number:

_____

USING THE STOOL COLLECTION KIT

Before you begin, review the following:

a. Make sure you have a *collection hat* and collection tube.
b. Make sure you are able to deliver the sample to City of Hope within 1 week.

STEP ONE: Please place the *collection hat* around the rim of your toilet seat for stool collection. 	
STEP TWO: Unscrew the collection tube cap and use the spoon to scoop one spoonful of feces (about the size of a quarter) from a sample. Place the sample in the collection tube. Tighten the cap and shake to mix the contents thoroughly (invert 10 times) to create a suspension. Note: Some fecal material may be difficult to re-suspend. As long as the material is suspended, the sample is stabilized. Foaming/frothing during shaking is normal.	 Scoop a portion of the stool sample into the DNA/RNA Shield™ Fecal Collection Tube

STEP THREE: Wash hands well, and write today's date on the label.	
STEP FOUR: Place the plastic tube in the bag, and seal the back using the adhesive tape already present on the bag.	
STEP FIVE: Bring the sample to your City of Hope appointment.	**THANK YOU FOR YOUR PARTICIPATION!**

Appendix P: Diet and Stool Frequency Log

DIET and STOOL FREQUENCY LOG - GENERAL INSTRUCTIONS

As a part of your participation in the current study, we are requesting that you complete a study log every day.

General pointers:

- When you come to the clinic, bring your logs with you.
- Each page has room for seven days – one row should be completed for each day.
- Please **avoid any intake of yogurt, yogurt-containing foods, or other bacteria-fortified foods**.

Example of how the top part of the log will look:

- A study team member will complete the information in this box before you leave the clinic.

COMPLETED BY STUDY TEAM	Participant Initials: JSM	Participant Research Number: 1001	Group: A

Example of how the information you enter might look:

- You or someone close to can complete the log for you, so long as the information is correct.
- List all prescription and non-prescription medications.
- The person who completes that day's entry should write his or her initials in the last column.

Day and Date	General description of food I ate:	*Did I eat yogurt or take probiotics?*	*How was my stool frequency?*	*Was a stool sample collected?*	*Medications taken*	*Initials of person filling information*
	Eggs, toast, juice Ham sandwich, coke, potato chips Steak, mashed potatoes, wine	○ Yes ☒ No	☒ Seems like baseline ○ 1-3 stools more than baseline ○ 4-6 stools more than normal ○ 7 or more than baseline, or incontinence	○ Yes ☒ No	Vitamin C, Lipitor	JBC
			○ Seems like baseline			

Example of the signature line:

- When you hand over the document to the study team, they will ask to sign and date at the bottom of each log if you agree that the information is complete and correct.

At the time of handing over the document -- Participant Signature: Joseph Black Smith Date 12/18/2002

COMPLETED BY STUDY TEAM	Participant Initials:	Participant Research Number:

Day and Date	General description of food I ate:	*Did I eat yogurt or take probiotics?*	*How was my stool frequency?*	*Was a stool sample collected?*	*Medications taken*	*Initials of person filling information*
	Eggs, toast, juice Ham sandwich, coke, potato chips Steak, mashed potatoes, wine	○ Yes ☒ No	☒ Seems like baseline ○ 1-3 stools more than baseline ○ 4-6 stools more than normal ○ 7 or more than baseline, or incontinence	○ Yes ☒ No	Vitamin C, Lipitor	JBC
		○ Yes ○ No	○ Seems like baseline ○ 1-3 stools more than baseline ○ 4-6 stools more than normal ○ 7 or more than baseline, or incontinence	○ Yes ○ No		
		○ Yes ○ No	○ Seems like baseline ○ 1-3 stools more than baseline ○ 4-6 stools more than normal ○ 7 or more than baseline, or incontinence	○ Yes ○ No		
		○ Yes ○ No	○ Seems like baseline ○ 1-3 stools more than baseline ○ 4-6 stools more than normal ○ 7 or more than baseline, or incontinence	○ Yes ○ No		
		○ Yes ○ No	○ Seems like baseline ○ 1-3 stools more than baseline ○ 4-6 stools more than normal ○ 7 or more than baseline, or incontinence	○ Yes ○ No		
		○ Yes ○ No	○ Seems like baseline ○ 1-3 stools more than baseline ○ 4-6 stools more than normal ○ 7 or more than baseline, or incontinence	○ Yes ○ No		

		○ Yes ○ No	○ Seems like baseline ○1-3 stools more than baseline ○4-6 stools more than normal ○7 or more than baseline, or incontinence	○ Yes ○ No		

At the time of handing over the document -- Participant Signature: _____ Date _____

Appendix Q: At Home Sample Collection Kit Contents

Contents of each kit to be provided to participants for at home collection:

[] Copy of Appendix O: Instructions for Stool Specimen Collection

[] Stool collection hat
[] Specimen tube with label attached
- **Label should have participant identifier added;** the participant will be asked to add the date himself/herself.

[] Plastic sealable bag

Appendix R: Checklist for study nurses, including documentation of patient's primary language for Geriatric Assessment

Patient's name and MRN_____
Patient's primary language_____

	Pre-study (up to 28 days prior to enrolling)[i]	C1D1 (28 day cycle)	C1D8 (± 1 day)	C1D15 (± 1 day)	C2D1 (± 3 days)	C2D15 (±3 days)	C3D1 (± 3 days)	C4D1 (± 3 days)	C5D1 (± 3 days)	C6D1 (± 3 days)	Every cycle thereafter (± 3 days)	Every 3 cycles (± 7 days)	Off treatment[h]
Diarrhea Checklist		☐[l]											
Nurse brief toxicity evaluation		☐	☐	☐	☐	☐	☐						
Adherence evaluation (pill count, diaries) (± 1 week)		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
Tumor measurements using CT or PET-CT (± 1 week)	☐[d]							☐				☐[e]	☐[f]
Geriatric Assessment Survey (±1 week)	☐							☐					☐[g]

d: Baseline assessment may be done up to 30 days prior to study enrollment.

e: Tumor measurements are repeated every 3 cycles ± 1 wk until patient comes off study. Documentation (radiologic or clinical) must be provided for patients removed from study for progressive disease.

f: Off-study radiologic evaluation will only be done if clinically indicated.

g: Geriatric assessment will be performed at baseline prior to study, after 3 cycles and at the end of study. Geriatric assessment will be repeated off study ONLY if it had not been administered within the previous month. If patient's native language is not covered by the current language forms, geriatric assessment form can be omitted with clear documentation.

h: Patients will be followed for 30 days following discontinuation of therapy in order to capture toxicity attributable to therapy.

i: Chart review data must be within 28 days to determine if patient meets study criteria. Once patient meets study criteria, then all criteria must be within window specified in protocol from Day 1 as indicated in column one in the schema above.

APPENDIX S: SAMPLE GUIDELINES

SAMPLES MUST BE DE-IDENTIFIED WITH NO PHI. AIM TO DELIVER SAMPLES ON A MONDAY THROUGH THURSDAY.

1. **Peripheral Blood Samples**:

Dr. Tim Synold
Cc: Lesley Smith-Powell
Analytical Pharmacology Core Facility (APCF)
Shapiro 1042
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010
Tel: 626-218-2954
tsynold@coh.org; Lsmith-Powell@coh.org

2. **Microbiome specimens:**

Dr. Cui Ke

CC: Biospecimen Coordinator

COH Biorepository Core

City of Hope National Medical Center

1500 E. Duarte Road

Duarte, CA 91010

626-218-1848; 626-218-0462

kcui@coh.org; spathan@coh.org

Approximately 30-50 samples stool samples will be temporarily stored at -80ºC in the Analytical Pharmacology Core Facility (APCF) in Shapiro 1042 (Dr. Tim Synold/Leslie Smith-Powell) until batch shipping to TGen:

Sarah Highlander, PhD, Director
TGen Clinical Microbiome Services Center
Pathogen and Microbiome Division
Translational Genomics Research Institute
3051 W. Shamrell Blvd., Suite 106
Flagstaff, AZ 86005
shighlander@tgen.org | 928-213-6996