Official Title	AN OPEN-LABEL, PHASE 2 BASKET STUDY OF NERATINIB IN PATIENTS WITH SOLID TUMORS WITH SOMATIC ACTIVATING *HER* MUTATIONS
NCT Number	NCT01953926
Version Date	03-FEB-2021

AN OPEN-LABEL, PHASE 2 BASKET STUDY OF NERATINIB IN PATIENTS WITH SOLID TUMORS WITH SOMATIC ACTIVATING *HER* MUTATIONS

Study Protocol Number:	PUMA-NER-5201
Disease Condition:	Solid tumors harboring somatic *HER* mutations
Sponsor's Investigational Product Name/Formulation:	Neratinib Tablets
US IND Number	107931
EudraCT Number	2013-002872-42
Lead Investigators:	

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Date of Protocol

Original	08-JUL-2013
Amendment 1	07-NOV-2013
Amendment 2	02-APR-2014
Amendment 3	17-MAR-2015
Amendment 4	20-MAY-2016
Amendment A4.1 (France)	27-FEB-2017
Amendment 5	04-OCT-2017
Amendment A5.1 (France)	26-MAR-2018
Amendment A5.2 (FLC, select sites)	20-APR-2018
Amendment 6	21-JAN-2020
Amendment A6.1 (France)	20-APR-2020
Amendment 7	03-FEB-2021

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STUDY CONTACTS

Refer to the study reference manual.

PROTOCOL SYNOPSIS

Title: An open-label, Phase 2 basket study of neratinib in patients with solid tumors with somatic activating *HER* mutations

Condition or Disease: Solid tumors harboring somatic activating *HER* mutations

Approximate Values			
Number of Patients	650	Duration of Patient Participation	18 months
Number of Centers	90	Duration of study	102 months

Objectives:

The objectives of this study, applicable to each cohort, are:

For the randomized hormone receptor positive (HR+), *HER2* negative metastatic breast cancer:

Primary:

- To determine the confirmed objective response rate (ORR) by independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Secondary:

- To determine the confirmed ORR by investigator
- To determine the duration of response (DOR) by both independent central review and investigator
- To determine the clinical benefit rate (CBR) by both independent central review and investigator
- To determine the progression-free survival (PFS) by both independent central review and investigator

For the metastatic cervical cancer cohort:

Primary:

- To determine the confirmed ORR by independent central review according to RECIST v1.1

Secondary:

- To determine the confirmed ORR by investigator
- To determine the DOR by both independent central review and investigator
- To determine the CBR by both independent central review and investigator
- To determine the PFS by both independent central review and investigator
- To determine overall survival (OS)

For all other cohorts:

Primary:

- To determine the first objective response rate (ORR_{first}) by investigator at the first post-baseline tumor assessment

Secondary:

- To determine the confirmed ORR by investigator
- To determine the DOR by investigator
- To determine the CBR by investigator
- To determine the PFS by investigator
- To determine OS

Safety Objectives:

For all cohorts, including the randomized HR+, *HER2* negative metastatic breast cancer and metastatic cervical cancer cohorts:

- To assess the safety profile and tolerability of study treatments

- To assess Patient Reported Outcomes (PRO)

Exploratory: The exploratory objectives of this study are:

- To collect and retrospectively evaluate somatic mutations or gene aberrations using next-generation sequencing (NGS) in the most recent pretreatment tumor biopsy or fresh tumor tissue biopsies at a central laboratory.
- To explore genetic modifiers of sensitivity and/or resistance to neratinib using molecular profiling techniques in pretreatment archival and/or fresh tumor specimens and paired normal whole blood.
- To evaluate cell-free DNA (cfDNA) from plasma specimens collected at baseline/screening, during the course of treatment, and upon disease progression to identify *HER2* and *EGFR* mutations and other gene aberrations and to assess any potential associations with neratinib sensitivity and/or primary/acquired resistance to neratinib or neratinib-containing therapy.
- To evaluate potential genes or protein biomarkers that may be reported to confer neratinib sensitivity and/or primary/acquired resistance to neratinib or neratinib-containing therapy from *optional* fresh core tumor biopsies during time of treatment and/or at the time of treatment discontinuation or disease progression.

Study Design:

This is an open-label, multicenter, multinational, Phase 2 study exploring the efficacy and safety of neratinib as monotherapy or in combination with other therapies in patients with *HER* (*EGFR*, *HER2*) mutation-positive solid tumors. Patients with tumors harboring somatic mutations in *HER* will be identified through previously documented mutation testing performed prior to screening. The presence of human *HER* mutations (*EGFR*, *HER2*) will be retrospectively confirmed by central testing via next generation sequencing (NGS). The study has a basket design and includes several cohorts, either defined by an actionable somatic mutation or by actionable mutation and tumor histology (for example *HER2* mutant cervical cancer). In the course of the study, enrollment in certain cohorts can be completed and enrollment in new cohorts initiated to test the anticancer effect of neratinib in other histologies, specific molecular abnormalities, and/or in combination with other drugs.

Patients with *HER2* mutant, *HER2* negative breast cancer will be divided into different treatment cohorts on the basis of HR status: HR negative (Triple Negative Breast Cancer [TNBC]) and HR+.

- Patients in the HR negative breast cancer cohort (TNBC) will receive neratinib in combination with trastuzumab.
- Patients in the HR+, *HER2* negative, *HER2* mutant breast cancer cohort with RECIST measurable tumors and who have been previously been treated with CDK4/6 inhibitors (CDK4/6i) will be randomized to receive single agent fulvestrant, fulvestrant in combination with trastuzumab, or neratinib in combination with trastuzumab and fulvestrant with a randomization ratio of 1:1:1. Randomization will be stratified by the number of lines of prior therapy for metastatic disease (≤ 2 and >2 lines) and by prior fulvestrant therapy.

  The randomized HR-positive (HR +), *HER2* negative, *HER2* mutant metastatic breast cancer cohort is designed to investigate the individual contribution of neratinib and/or trastuzumab to fulvestrant via Simon's 2 stage optimal design. The decision to carry over on enrollment of each arm in the cohort will be based on stage I and II analysis of Simon's 2 stage in consultation with the Independent Data Monitoring Committee (IDMC).

  - Patients in the HR+ cohort who receive single agent fulvestrant or fulvestrant plus trastuzumab will be eligible for triplet therapy (neratinib, fulvestrant, trastuzumab) upon progression. Patients who have unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease related symptoms before the first scan post-treatment are eligible for the triplet therapy. Efficacy will be determined based on response to initial regimen only.

- Patients in the HR+ breast cancer cohort who have not received prior CDK4/6i therapy (eg. CDK4/6i naïve) will receive neratinib in combination with trastuzumab and fulvestrant as part of an open label cohort.

The trial will consist of a screening period, a treatment period, and a follow-up period after the study therapy is discontinued for any reason. An end of treatment (EOT) assessment is performed 28 days (+14 days) after the last dose of investigational product(s) and adverse events are collected 28 days after the last dose of investigational product(s).

Neratinib will be administered orally with food once daily (recommended to be taken in the morning), on a continuous basis. Dose delays and modifications will be handled as per instructions in the package insert. All patients taking neratinib will maintain a patient diary for the study to record each dose of neratinib taken and while receiving antidiarrheal prophylaxis with loperamide taken for the first two cycles of treatment. For cohorts receiving combination treatment that includes trastuzumab, post-treatment radiographic evaluation of their disease will be conducted every 3 cycles. For all other cohorts, post-treatment disease assessment will be conducted every 2 cycles. Treatment should be administered until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms. Tumor markers or circulating tumor cells should not be used as the sole criteria for determining progression. At the time of decision regarding disease progression, radiological exam should be performed. Patients will continue study treatment until disease progression, unacceptable toxicity, patient withdrawal of consent, or death. Patients who develop disease progression, but in the opinion of the Investigator would still benefit from continuing study, may continue per-protocol therapy if approved by the Sponsor. Survival follow-up will be every 12 weeks after treatment discontinuation. Enrollment will continue as dictated by the Simon's 2-stage design in all the histology and mutation specific cohorts and/or up to 30 patients per cohort in multi-cancer, mutation specific NOS cohorts. Enrollment in the randomized breast cancer, non-randomized breast cancer and cervical cancer cohorts will also continue as dictated by the Simon's 2-stage design up to 50 patients per cohort.

Tumor Cohorts Open to Enrollment in Amendment 7

Randomized Breast Cancer Cohort

Tumor Cohort	Mutation	Randomized Treatment	Sample Size (# subjects)
Breast HR Positive (with prior CDK4/6i)	*HER2* mutant	• Fulvestrant: 500 mg on Study Day 1, 15, and 29; once every 28 days thereafter Or • Fulvestrant: 500 mg on Study Day 1, 15, and 29; once every 28 days thereafter • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks Or • Neratinib: 240 mg daily • Fulvestrant: 500 mg on Study Day 1, 15, and 29; once every 28 days thereafter • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks	Up to 18 Up to 18 Up to 50

Non-randomized Breast Cancer Cohorts

Tumor Cohort	Mutation	Assigned Treatment	Cohort Sample Size (# subjects)
Breast HR Positive (CDK4/6i naïve)	*HER2* mutant	• Neratinib: 240 mg daily • Fulvestrant: 500 mg on Study Day 1, 15, and 29; once every 28 days thereafter • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks	Up to 50
Breast TNBC (HR Negative)	*HER2* mutant	• Neratinib: 240 mg daily • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks	Up to 50

Cervical Cancer Cohort

Tumor Cohort	Mutation	Assigned Treatment	Cohort Sample Size (# subjects)
Cervical	*HER2* mutant	• Neratinib: 240 mg daily	50

Cohorts Not Receiving Trastuzumab

Tumor Cohort	Mutation	Assigned Treatment
Salivary Gland	*HER2* mutant	• Neratinib: 240 mg daily
Non-small Cell Lung	*EGFR* exon 18 mutations	• Neratinib: 240 mg daily

Tumor Cohorts Closed to Enrollment in Amendment 7

The following cohorts were closed to enrollment in Amendment 7: solid tumors (NOS) *HER2* mutant monotherapy and bladder/urinary *HER2* mutant combination therapy of neratinib + paclitaxel.

Investigational Product, Dose, and Administration:

- Neratinib: Patients will receive six 40-mg tablets (total daily dose 240 mg) administered orally, once daily with food (recommended to be taken in the morning), continuously.
- Fulvestrant: Patients will receive 500 mg total dose administered as two 5 mL injections, by intramuscular injection, one in each buttock on Days 1, 15, and 29; then once every 4 weeks thereafter; see fulvestrant package insert and Schedule of Procedures.
- Trastuzumab: Patients will receive an initial dose of 8 mg/kg of trastuzumab intravenously (IV) administered on Cycle 1 Day 1 (C1D1), followed by 6 mg/kg IV once every 3 weeks thereafter; see Herceptin (trastuzumab) package insert and Schedule of Procedures.

Study Population:

Inclusion Criteria for All Patients

Each patient will be entered into this study only if she/he meets all of these criteria:

1. Men and women who are ≥18 years old at signing of informed consent.
2. At the time of screening, histologically confirmed cancers in patients with previously documented activating *EGFR (exon 18)* or qualifying *HER2* mutation confirmed by a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalent laboratory, and who are refractory to standard therapy or for which standard or curative therapy does not exist or is not considered sufficient or appropriate

3. At least one measurable lesion, as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1; Eisenhauer et al, 2009).
4. Left ventricular ejection fraction (LVEF) ≥50% measured by multiple-gated acquisition scan (MUGA) or echocardiogram (ECHO).
5. Eastern Cooperative Oncology Group (ECOG) status of 0 to 2.
6. Female patients with cancers known to secrete β-human chorionic gonadotropin (hCG), ie germinomas, are eligible if the pattern of serum β-hCG is suggestive of the malignancy and the pelvic ultrasound is negative for pregnancy.
7. Male patients must agree and commit to use a barrier method of contraception while on treatment and for 3 months after the last dose of trastuzumab, fulvestrant, or neratinib monotherapy. Patients of child-bearing potential must agree and commit to the use of a highly effective double-barrier method of contraception (eg, a combination of male condom with an intravaginal device such as the cervical cap, diaphragm, or vaginal sponge with spermicide) or a non-hormonal method, from the signing of the informed consent until:
   i. 28 days after the last dose of neratinib monotherapy, or
   ii. 7 months after last dose of trastuzumab or
   iii. 1 year after the last dose of fulvestrant.
8. Provide written, informed consent to participate in the study and follow the study procedures.
9. Agree to provide most recent metastatic tumor sample or fresh tumor biopsy, and plasma/blood specimens for gene sequencing and other biomarker analysis.

Additional Inclusion Criteria for all Breast Cancer Patients that Harbor *HER2* Mutations and NCSLC Patients that Harbor *EGFR* exon 18 Mutations

10. Must provide a pretreatment fresh biopsy within 28 days prior to starting treatment unless the biopsy procedure presents a safety concern for the patient as determined by the Investigator, or other exceptional reason upon agreement with the Sponsor

Additional Inclusion Criteria for HR+ Breast Cancer Patients with Tumors that Harbor *HER2* Mutations

11. HR+ disease defined as ≥1% estrogen receptor (ER) positive and/or progesterone receptor (PR) positive cells (performed on the most recent biopsy as assessed locally and consistent with current American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) or European Society of Medical Oncology (ESMO) guidelines):
12. Biopsy from a non-bony metastatic site: preferred, or
    a. Biopsy from bony metastasis or if the sample is considered inadequate or unavailable: assessment of HR status will be at the Investigator's discretion.
13. Postmenopausal, as defined by at least one of the following criteria:
    a. Age ≥60 years;
    b. Age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and serum estradiol and follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females;
    c. Documented bilateral oophorectomy,
14. Medically confirmed ovarian failure

    OR
15. Pre/perimenopausal, ie, not meeting the criteria for being postmenopausal:
    a. Pre/perimenopausal women can be enrolled if amenable to be treated with a luteinizing hormone receptor hormone (LHRH) agonist. Patients must have commenced treatment with an LHRH agonist at least 4 weeks prior to the first dose of neratinib.
16. Prior treatment with chemotherapy or hormonal therapy (including fulvestrant).

Exclusion Criteria for All Patients

A patient will be excluded from this study if she/he meets any of these criteria:

1. Patients harboring ineligible somatic *HER2* mutations, such as those that are subclonal in nature or those resulting in the expression of truncated proteins including alterations that result in premature stop codon or a change in reading frame (ie, frame shift mutations).
2. Prior treatment with any pan-*HER, HER2-,* or *EGFR* tyrosine kinase inhibitor (TKI) (eg, lapatinib, afatinib, dacomitinib, neratinib, tucatinib, poziotinib, gefitinib, erlotinib, osimertinib) is excluded with the following exception: patients with *EGFR* exon 18 mutated non-small cell lung cancer (NSCLC) who may have received afatinib, osimertinib, or other pan-*HER* or *EGFR* TKIs remain eligible.
3. Not recovered to at least Grade 1 at screening (Common Terminology Criteria for Adverse Events v4.0 [CTCAE v4.0]) from all clinically significant adverse events related to prior therapies (excluding alopecia).
4. Received chemotherapy or biologic therapy ≤2 weeks or 5 half-lives (t½) of the agent used, whichever is shorter, prior to the initiation of investigational product.
5. Received radiation therapy ≤14 days prior to initiation of investigational product.
6. Patients who are receiving any other anticancer agents with the exception of patients on 1) a stable dose of bisphosphonates or denosumab or 2) sex hormone therapy in the case of breast, or gynecological cancers.
7. Received prior therapy resulting in a cumulative epirubicin dose >900 mg/m^2 or cumulative doxorubicin dose >450 mg/m^2. If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 450 mg/m^2 doxorubicin.
8. Symptomatic or unstable brain metastases. (Note: Asymptomatic patients with metastatic brain disease who have been on a stable dose of corticosteroids for at least 14 days are eligible to participate in the study.)
9. Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2), unstable angina (symptomatic angina pectoris within the past 180 days that required the initiation of or increase in anti-anginal medication or other intervention), myocardial infarction within 12 months of enrollment, or ventricular arrhythmia (except for benign premature ventricular contractions).
10. Demonstrates a QTc interval >450 ms for men or >470 ms for women or known history of congenital QT-prolongation or Torsade de pointes (TdP).
11. Inadequate bone marrow, renal or hepatic function as defined on screening laboratory assessments outside the following limits:

Laboratory Assessments Endpoints

Laboratory endpoint	**Required limit for exclusion**
Absolute neutrophil count (ANC)	<1,000/µL (1.0 x 10^9 /L)
Platelet count	<100,000/µL (<100 x 10^9/L)
Hemoglobin	<8 g/dL (transfusion allowed to treat low hemoglobin) Transfusion must be at least 7 days prior to C1D1.
Total bilirubin	>1.5 x institutional upper limit of normal (ULN) (in case of known Gilbert's syndrome, >2x ULN)
Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)	>3 x institutional ULN OR >5 x ULN if liver metastases are present

Creatinine	>1.5 x institutional ULN OR Calculated Creatinine Clearance <30 mL/min (as measured directly with a 24-hour urine or calculated by Cockcroft-Gault formula [a] or Modification of Diet in Renal Disease [MDRD] formula [b])

[a] Cockcroft and Gault, 1976.

[b] Levey et al, 1999.

12. Active infection or unexplained fever >38.5°C (101.3°F).
13. Women who are pregnant, are planning on becoming pregnant, or are breast-feeding.
14. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (eg, Crohn's disease, malabsorption, or Grade ≥2 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE version 4.0] diarrhea of any etiology at baseline.
15. Clinically active infection with a hepatitis virus.
16. Evidence of significant medical illness, abnormal laboratory finding, or psychiatric illness/social situations that could, in the Investigator's judgment, make the patient inappropriate for this study.
17. Known hypersensitivity to any component of the investigational product, required combination therapy, or loperamide.
18. Unable or unwilling to swallow tablets.
19. Patients with known activating *KRAS* mutations.

Additional Exclusion Criteria for Patients with Breast Cancer With *HER2* Mutations

20. Patients with known *HER2*+ tumors (protein overexpression or gene amplification as defined by ASCO/CAP guidelines or HER2 amplifications as determined by copy number alterations by NGS) are excluded.

Additional Exclusion Criteria for Patients With *HER2* Mutations Treated With Trastuzumab Combination Therapy or Being Randomized into HR+ Breast Cancer Cohorts

21. Hypersensitivity to trastuzumab, murine proteins or any of the excipients listed in the Herceptin label.
22. Severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy

Efficacy Assessments:

For cohorts receiving combination treatment that includes trastuzumab, post-treatment disease assessment by CT or magnetic resonance imaging (MRI) will be conducted at the beginning of Week 10 (ORR_{first}), and every 3 cycles (± 7 days) thereafter (see Schedule of Procedures, Appendix 1 Table A1.1). For all other cohorts not receiving trastuzumab, post-treatment disease assessment will be conducted at the beginning of Week 9 (ORR_{first}), and every 2 cycles (± 7 days) thereafter (see Schedule of Procedures, Appendix 1 Table A1.2). Complete or partial response (CR or PR) must be confirmed with a repeat scan performed no sooner than 4 weeks after the criteria for response are first met. In cases where the subject discontinues treatment for reasons other than progressive disease (eg., adverse event, patient choice, noncompliance, etc.) and the response is either CR or PR, then a confirmation scan is required no sooner than 4 weeks after the criteria of response is met. Radiological response is assessed by RECIST v1.1. Following one year on therapy, scans may move to every 4 cycles for trastuzumab-containing regimens and every 3 cycles for non-trastuzumab containing regimens. Following two years on therapy, scans may move to every 5 cycles for trastuzumab-containing regimens and every 4 cycles for non-trastuzumab-containing regimens.

Safety Assessments:

Patients receiving at least one dose of the investigational products will be evaluable for safety.

Safety will be assessed based on medical history, vital sign measurements, physical examination findings, electrocardiogram (ECG) results, cohort specific MUGA or ECHO, laboratory assessments, and adverse events.

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria (NCI CTC) version 4.0. Adverse events and serious adverse events will be reported until 28 days after the last dose of investigational product(s) and will be followed until resolution or until condition stabilizes.

Should an Investigator be made aware of any serious adverse events occurring any time after the reporting period that may be causally related to the administration of neratinib, it should be promptly reported. In addition to cardiac evaluations conducted during the study, patients who are receiving trastuzumab are required to be followed-up for potential cardiac toxicity (as assessed by MUGA or ECHO scans, see Schedule of Procedures, Appendix 1 Table A1.1 and Table A1.2) every 6 months and up to 24 months after the last dose of trastuzumab.

Other Assessments:

The most recent metastatic tumor tissue will be obtained for all patients and banked by the sponsor for retrospective centralized confirmation of somatic mutations in the ERBB gene family (*EGFR*, *HER2*). This tumor sample should preferably be from the specimens used to detect the initial mutation prior to study enrollment. For patients that do not have an archived tumor tissue, a fresh biopsy will be obtained if medically feasible. For all breast cancer cohorts and NSCLC exon 18 mutations cohort, a fresh pretreatment tumor biopsy collection is mandated unless the biopsy procedure presents a safety concern for the patient.

Whole blood for germline DNA analysis will be collected once at screening. Cell-free DNA will be obtained from plasma samples collected at screening, on-treatment in accordance with the Schedule of Procedures (Schedule of Procedures, Appendix 1 Table A1.1 and Table A1.2), and at the time of treatment discontinuation; cfDNA will be subject to molecular profiling to identify *HER2* and *EGFR* mutations and other gene aberrations related to treatment response and resistance.

Health-related Quality of Life Assessment

The following patient-reported outcomes will be assessed for all patients: the FACT-G questionnaire. Patient-reported outcome assessments will be collected at screening, and at the beginning of each cycle for up to 6 months or EOT, whichever comes first.

Statistical Methods:

Sample Size Justification for the Randomized HR+ Breast Cancer Study Cohort:

A Simon's 2-stage optimal design (Simon, 1989) will be used to determine whether there is sufficient activity to warrant further development of the therapy and to minimize the number of patients exposed to therapy if ineffective. For each treatment arm, using Simon's 2-stage optimal design (with significance level 10% and power of 80%), an ORR (confirmed) of 10% or less per RECIST by independent assessment will be considered unacceptable (null hypothesis) whereas an ORR (confirmed) of 30% per RECIST by independent assessment will merit further study (alternative hypothesis). In the first stage, 7 patients are enrolled in each treatment arm. If at least 1 response is observed in the first stage, the second stage will be opened. In the second stage, 11 additional response evaluable patients will be accrued and randomized for a total of 18 patients in the treatment arm. The null hypothesis will be rejected (for each arm separately) if at least 4 responses are observed in Stage 2 for each arm.

Once the Simon's 2-stage criteria are met, enrollment of the neratinib arm may continue until up to 50 patients have been enrolled.

Sample Size Justification for All Other Cohorts:

A Simon's 2-stage optimal design (Simon, 1989) will be used to determine whether neratinib monotherapy has sufficient activity to warrant further development in the following cohorts: cervical, salivary gland, and *EGFR* exon 18 non-small cell lung cancers. A similar Simon's 2-stage design will be used to determine whether neratinib combination therapy has sufficient activity to warrant further development in the following cohorts: HR+ and CDK4/6i naïve and TNBC. Early study termination will be permitted if data at the first stage indicate that the treatment is ineffective. For each cohort, using Simon's optimal 2-stage design (with significance level 10% and power of 80%), an ORR_{first} of 10% or less will be considered unacceptable (null hypothesis) whereas an

ORR_{first} of 30% will merit further study (alternative hypothesis). In the first stage, enrollment will continue until 7 patients received at least one dose of study treatment and completed the first tumor assessment by the investigator (response evaluable). If no responses are observed, the second stage for the cohort must be discontinued. Otherwise 11 additional response evaluable patients will be accrued for a total of 18 patients in the cohort. The null hypothesis will be rejected (for each cohort separately) if at least 4 responses are observed in Stage 2 for each cohort.

Once the Simon's 2-stage criteria are met, enrollment into the salivary gland and *EGFR* exon 18 mutant NSCLC cohorts may continue until up to 30 patients; and the enrollment into the cervical, HR+ CDK4/6i naïve, and TNBC cohorts may continue up to 50 patients. A new cohort may also be opened separately at any time per Sponsor discretion and follow the Simon's 2-stage criteria. Cohorts may close prior to planned enrollment.

Statistical Analysis

In general, efficacy and safety analyses in this study are cohort-specific and will be summarized by monotherapy and combination therapy separately. Safety analyses will also be summarized across some cohorts where appropriate. Integrated analysis of HR+ metastatic breast cancer patients receiving neratinib, fulvestrant, and trastuzumab from either the randomized cohort or the original cohort will be performed.

Categorical variables will be summarized using counts and percentages. Percentages will be displayed to 1 place after the decimal point (xx.x), with the exception of 100%, which will be displayed without additional decimal places. Continuous variables will be summarized using number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum.

The binary endpoints (eg, ORR_{first}, ORR, CBR) will be estimated and its associated two-sided 95% Clopper-Pearson confidence intervals will be determined.

Time to event endpoint (eg, PFS, OS, DOR) will be estimated via Kaplan-Meier with its associated two-sided 95% confidence intervals.

Patient-reported outcomes will be summarized and plotted over time. Changes from baseline will be provided with both point estimates and confidence intervals.

Safety:

All patients who receive at least one dose of the investigational product will be analyzed for safety by cohort and across some cohorts where appropriate. Safety endpoints will be summarized descriptively for vital signs, adverse events, laboratory tests, and ECG. Serious adverse events, deaths, and patients discontinued from study treatment will be listed. The IDMC will oversee the safety of patients during the study.

Interim Analysis

Interim analyses may be performed at the completion of each stage for cohorts with a Simon's 2-stage design and for other cohorts as necessary. An IDMC will be established to regularly review accumulating safety data and efficacy data throughout the study.

Primary Analysis

The primary analysis will be performed when all enrolled patients have been followed for at least 6 months or when all responses have had a chance to be confirmed.

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ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration-versus-time curve; exposure
BID	twice a day
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CBR	clinical benefit rate
cfDNA	cell-free DNA
CFR	Code of Federal Regulations
C_{max}	maximum plasma drug concentration
CR	complete response
CRF	case report form
CS	clinically significant
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor (also known as HER1)
EIU	exposure-in-utero
EORTC	European Organization for Research and Treatment of Cancer
EOS	end of study
EOT	end of treatment
^{18}F-FDG	^{18}F-fluorodeoxyglucose
ER	estrogen receptor
ERBB	human protein product of the ERBB gene (also known as HER)
ERBB2	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2
EU	European Union
FLC	fibrolamellar carcinoma
GCP	Good Clinical Practice
Hb	hemoglobin
hCG	human chorionic gonadotropin
Hct	hematocrit
HER	human epidermal growth factor receptor
HR	hormone receptor

IB	Investigator's Brochure
IC_{50}	concentration at which there is 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation or International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IM	intramuscular(ly)
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat; intention-to-treat
IV	intravenous(ly)
LD	longest diameter
LDH	lactate dehydrogenase
LLN	lower limit of normal
LV	left ventricle
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters mercury
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multi-gated acquisition scan
NCI	National Cancer Institute
NCS	not clinically significant
NGS	next-generation sequencing
NOS	not otherwise specified
NSCLC	non-small cell lung cancer
ORR	objective response rate
ORR_{first}	objective response rate at the first post-baseline tumor assessment timepoint
OS	overall survival
PAC	Picture Archival Communication
PB-272	neratinib
PD	progressive disease
PET	positron emission tomography
PET/CT	^{18}F-fluorodeoxyglucose positron emission tomography combined with computerized tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PI3K	phosphoinositide-3 kinase
PK	pharmacokinetic
PLC	phospholipase C
PPI	proton pump inhibitor
PR	partial response
QID	four times a day

QTc	corrected QT interval
RANK	receptor activator of nuclear factor kappa-B
RAS	rat sarcoma (family of ras genes)
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
ROI	region of interest
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	stable disease
SOC	system organ class
SUL	standard uptake value normalized by lean body mass
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TdP	Torsade de Pointes
TEAE	treatment-emergent adverse event
TID	three times a day
TKI	tyrosine kinase inhibitor
T_{max}	time to peak concentration
ULN	upper limit of normal
US	United States (of America)
WBC	white blood cell
WHO Drug	World Health Organization Drug Reference List
WT	wild type

1. INTRODUCTION

1.1. The Epidermal Growth Factor Receptor (ERBB) Family

The epidermal growth factor receptor (EGFR) class of receptor tyrosine kinases (RTKs) comprises four receptor proteins encoded by four genes (in parentheses): EGFR (*EGFR*), *HER2* (ERBB2[Neu]), *HER3* (*ERBB3*) and *HER4* (*ERBB4*), together known as the HER protein family. Canonically, HER family proteins exist as inactive monomers until bound to ligand. Ligand binding prompts a conformational change and enables homodimerization or heterodimerization with another HER protein, leading to transphosphorylation and downstream signaling (reviewed by Yarden and Sliwkowski, 2001). EGFR binds to and is activated by a number of ligands, including EGF, TGFα, HB-EGF, amphiregulin, betacellulin, epiregulin, and epigen (Yarden and Sliwkowski, 2001; Jones et al, 1999). *HER3* and *HER4* bind to ligands in the neuregulin family, including heregulin (reviewed in Stove and Bracke, 2004). A ligand for *HER2* has not been identified; however *HER2* can still homodimerize (Ghosh et al, 2011; Peckys et al, 2015) and has been characterized as the preferred dimerization partner for EGFR and HER3 (Graus-Porta et al, 1997; Zaczek et al, 2005). In contrast, *HER3* does bind ligand, but lacks intrinsic kinase activity (Pinkas-Kramarski et al, 1996). Despite the lack of ligand binding and kinase activity in *HER2* and *HER3*, respectively, *HER2-HER3* heterodimers possess the most potent mitogenic activity among the HER family hetero- and homodimer combinations (Okines et al, 2011). Alterations within the HER family of RTKs have been reported in a number of tumor types. Oncogenic HER kinase alterations include receptor overexpression, elevated ligand levels, and somatic activating mutations. Sustained activation of HER signaling due to such alterations can result in oncogene or pathway-addicted tumors, and selective HER kinase inhibitors are now a component of standard treatment for several malignancies.

1.1.1. Somatic Mutations in *ERBB2*

Mutations in the *ERBB2* gene have been identified in multiple tumor types (Figure 1), and cluster primarily in the kinase domain at exons 19 and 20 (between amino acids 737-831) and the extracellular domain at exon 8 (amino acids 301-340) (Figure 2). The latter induce kinase activation by elevating C-terminal tail phosphorylation or by covalent dimerization via intermolecular disulfide bond formation (Greulich et al, 2012).

Activating point mutations in the *ERBB2* gene that have been associated with primary breast cancer include but are not limited to amino acid positions G309, S310, R678, L755, D769, V777, V842, and E930. Activating insertions/deletions associated with breast cancer include but are not limited to L755_T759del, and 774-755 and 776 in-frame insertions. Activating mutations in the *ERBB2* gene associated with colorectal cancer may include S310F, L755S, V777L, V842I, and L866M (Kavuri et al, 2015).

Figure 1: Frequency and Location of *ERBB2* Mutations in Cancer Biopsy Samples (*ERBB2* Amplification and Mutations across Cancer Types)

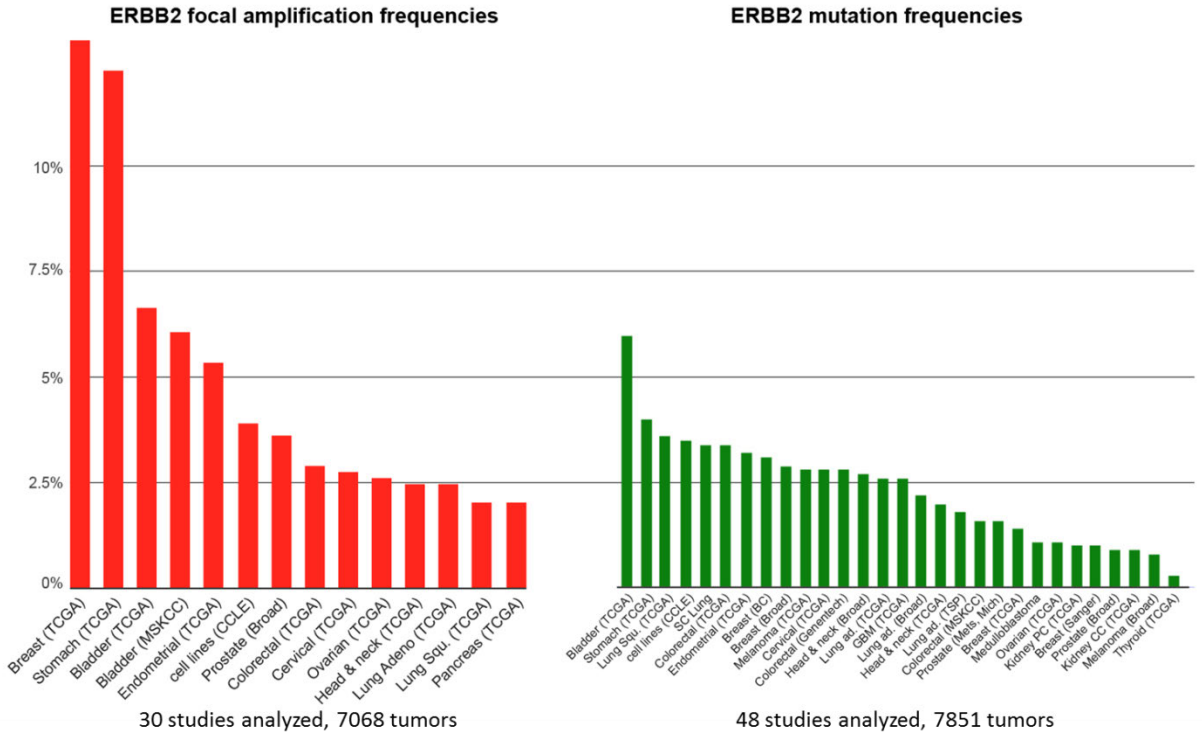
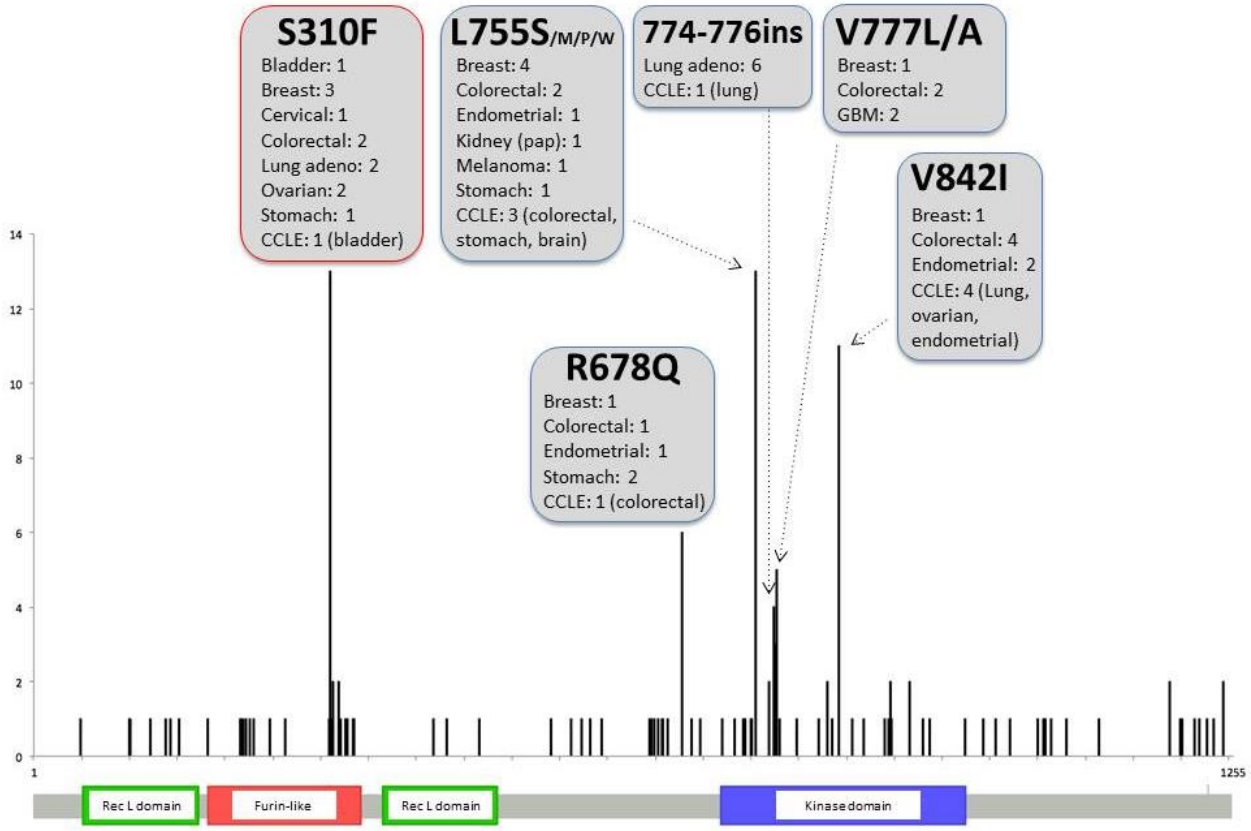


Figure 2: Frequency and Location of *ERBB2* Mutations in Cancer Biopsy Samples (*ERBB2* Mutation Hotspots across Cancer Types)



Reference: Figures duplicated with permission from Dr. Solit (www.iom.edu/Activities/Disease/NCPF/2013-FEB-11/Day%201/Session%204/17-Solit.aspx [accessed 21OCT2013]).

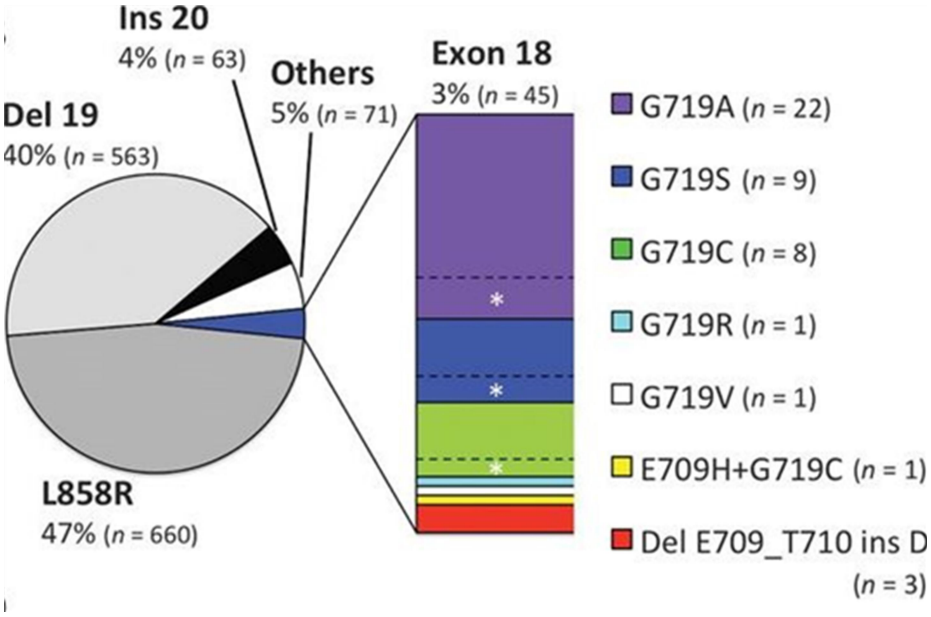
1.1.2. Somatic *EGFR* Exon 18 Mutations in Lung Cancer

Somatic mutations in the *EGFR* kinase domain have been identified in approximately 40% and 17% of patients with NSCLC in Asian and American patients, respectively (Yatabe et al, 2015; Kris et al, 2014).

EGFR exon 18 mutations, which are much less common, occur in 3-5% of all *EGFR*-mutant lung cancers (Kris et al, 2014; Cheng et al, 2015; Kobayashi et al, 2015; Lai et al, 2017).

At the Aichi Cancer Center, mutation analyses of tumor samples identified 1,402 *EGFR* mutation-positive lung cancers (Kobayashi et al, 2015, Figure 3). Most tumors harbored mutations such as deletion of exon 19 (40%) or L858R (47%). Exon 18 mutations, comprising of G719X (n=41), E709X+G719X (n=1), and deletion of exon 18 (n=3), were present in 3.2% (n=45) of tumor samples.

Figure 3: Distribution of *EGFR* Mutations in Lung Cancers (Aichi Cancer Center)



EGFR exon 18 mutations accounted for 4.1% of all *EGFR* mutations spanning from exons 18 through 21 from analysis of the publicly available COSMIC database (Kobayashi et al, 2015). Furthermore, mutations at codon 709 and 719 accounted for 84% of mutations in exon 18 (Figure 4). At codon 709, the delE709_T710insD mutation was the most frequently reported deletion, and the E709K and G719A mutations were the most frequent point mutations at codon 709 and 719, respectively (Figure 5).

Figure 4: Distribution of *EGFR* Exon 18 Mutations (COSMIC Database)

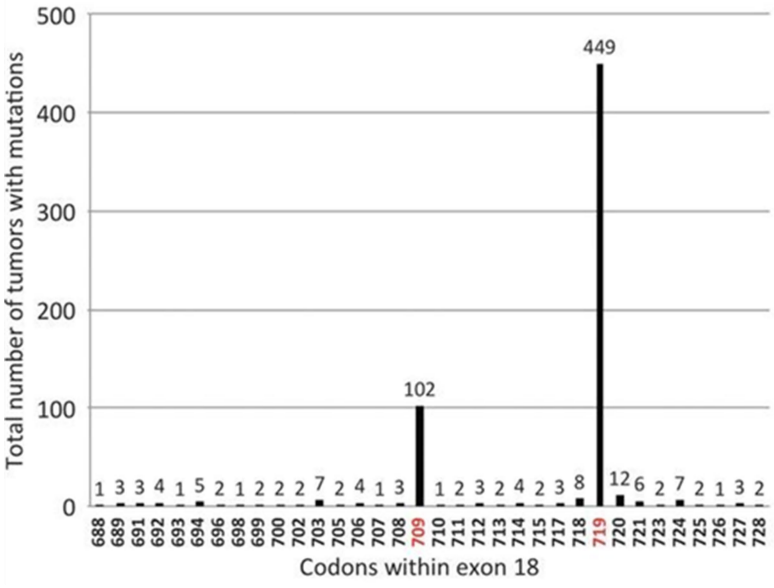
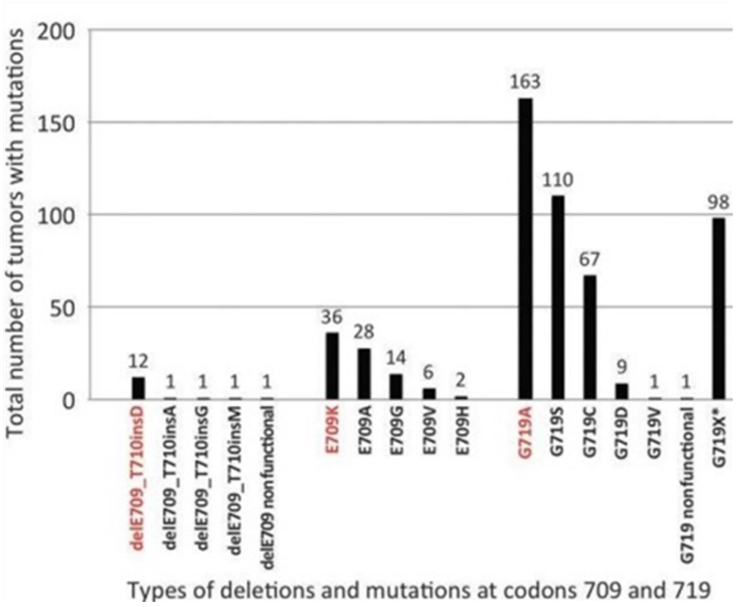


Figure 5: Distribution of Mutations at Codons 709 and 719 in *EGFR* Exon 18 (COSMIC Database)



1.2. Neratinib as a Cancer Therapy That Targets *ERBB* Receptors

1.2.1. Neratinib, An Irreversible Inhibitor of *EGFR*, *ERBB2*, and *ERBB4* Receptor Tyrosine Kinases

Neratinib (PB-272) is an orally available, small molecule, irreversible tyrosine kinase inhibitor (TKI) of *EGFR*, *ERBB2*, and *ERBB4*. Preclinical characterization showed that neratinib inhibits *EGFR* and *ERBB2* phosphorylation, downstream signaling, and cell growth in *EGFR*- and HER*2*-dependent cell lines, and decreased tumor formation in HER*2*-dependent xenograft models (Rabindran et al, 2004).

A summary of preclinical studies, human pharmacokinetic studies, and previous clinical studies of neratinib for treatment of *HER2*+ breast cancer is provided in the Investigator's Brochure (Neratinib IB).

On 17-JUL-2017, the United States (US) Food and Drug Administration (FDA) approved neratinib (NERLYNX™) for the extended adjuvant treatment of adult patients with early stage *HER2*-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy. On 25-FEB-2020, the FDA approved neratinib for use in combination with capecitabine, for the treatment of adult patients with advanced or metastatic *HER2*+ breast cancer who have received two or more prior anti-*HER2* based regimens in the metastatic setting.

1.2.2. Neratinib Treatment for ERBB2 Mutant Solid Tumors

Several preclinical studies have shown utility of neratinib in *ERBB2*-mutant, tumor models. Survival of Ba/F3 cells transformed by *ERBB2* wild type (WT) or G309E, S310F, S310Y, S312G, or A775_G776insYVMA mutant alleles was inhibited by neratinib (Greulich et al, 2012).

A seminal publication by Ron Bose and colleagues (Bose et al, 2013) identified 25 cases of breast cancer patients with *ERBB2* mutations reported in American Society of Clinical Oncology (ASCO) Group Z1031 Clinical Trial or The Cancer Genome Atlas (TCGA) Breast Cancer Database. Seven of these mutations, including five in the kinase domain (V777L, D769H, V842I, L755S, L755_T759del), one in the extracellular domain (G309A), and one in the intracellular juxtamembrane region (R687Q) were introduced into MCF10A, MCF7, and NIH 3T3 cell lines using retroviral vectors. The V777L, D769H, and V842I mutants strongly increased ERBB2 autophosphorylation and substrate protein (phospholipase C1, PLC) phosphorylation relative to WT ERBB2. Modest increases in ERBB2, PLC, and EGFR phosphorylation were reported with G309A, L755S, and R678Q. ERBB2 L755_T759del showed a marked decrease in ERBB2 and PLC phosphorylation, but an increase in EGFR phosphorylation, suggesting that L755_T759del may have the ability to activate other ERBB family members. Soft agar growth of cells expressing these mutants with the tyrosine kinase inhibitors lapatinib or neratinib revealed that all mutants were sensitive to neratinib, even the lapatinib-resistant L755S and L755_T759del mutations (Bose et al, 2013).

Examination of HER2-targeted therapies on the growth of colorectal cancer patient-derived xenografts harboring *ERBB2* mutations (S310Y, L866M, and V777L) showed that single agent therapy (trastuzumab, neratinib, or lapatinib) delayed tumor growth while dual HER2-targeted therapy with trastuzumab plus tyrosine kinase inhibitors caused tumor regression (Kavuri et al, 2015).

In summation, the preclinical experience suggests that cancer patients with solid tumors harboring activating *ERBB2* mutations could potentially benefit from treatment with neratinib.

1.2.3. Neratinib Treatment for *EGFR* Exon 18 Mutations in Lung Cancer

Neratinib has potent irreversible EGFR binding properties. EGFR exon 18 mutations, including G719, E709, and Del18 mutations, are observed less frequently (3%) in lung cancers and have poor response to first generation tyrosine kinase inhibitors (Kobayashi et al, 2015; Greulich et al, 2005). Preclinical studies suggest that *EGFR* exon 18 mutations display enhanced sensitivity to irreversible pan-HER inhibitors, including neratinib, as compared to approved benchmark EGFR TKIs including gefitinib and erlotinib (Kobayashi et al, 2015). Clinical responses to neratinib treatment have been previously reported in NSCLC patients harboring *EGFR* exon 18 mutations (Sequist et al, 2010). Here, we propose targeting these rare mutations in non-small cell lung cancer patients that may not benefit from currently approved EGFR TKIs.

1.3. Neratinib Phase 1 and Pharmacokinetic Data

Clinical pharmacokinetic (PK) results from the first-in-human study with ascending single and multiple doses in subjects with cancer showed that absorption of neratinib was slow with time to peak concentration (T_{max}) ranging from 3-6.5 hours post dose. After single or multiple daily oral doses of neratinib with food, the maximum plasma drug concentration (C_{max}) and the area under the plasma concentration-versus-time curve (AUC) increased with increasing dose. Furthermore, no major accumulation was observed when comparing Day 14 exposure with Day 1 exposure following once-daily dosing of neratinib 240 mg and 360 mg with food. The mean half-life ($t_{1/2}$) following a single dose on Day 1 ranged from 8 to 17 hours, which supports once-daily dosing of neratinib. 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 (Neratinib IB).

Data from a Phase 1 dose-escalation study in patients with advanced solid tumors demonstrated the safety and feasibility of once-daily oral treatment with neratinib. The maximum tolerated dose (MTD) was initially determined to be 320 mg. The higher frequency of high-grade diarrhea for subjects who received neratinib 320 mg in a subsequent Phase 2 study (46.2% at 320 mg daily vs 22.7% at 240 mg daily) led to the decision to reduce the recommended dose for neratinib to 240 mg (Neratinib IB).

In healthy subjects, a high-fat meal increased neratinib peak and total exposure (C_{max} and AUC_{inf}) by approximately 2-fold, and a standard breakfast increased neratinib exposure by 13%-17%, compared with exposure under fasting conditions (Neratinib IB).

Neratinib, a substrate of cytochrome P450 enzyme (CYP), is susceptible to interaction with potent CYP3A4 inducers or inhibitors such as rifampin and ketoconazole, respectively. In a clinical study in healthy subjects, exposures of neratinib were substantially reduced when neratinib was coadministered with rifampin. Ketoconazole was found to increase exposure to neratinib by ~481% in healthy subjects. Nonclinical in vitro experiments indicate that neratinib inhibits the transport of P-glycoprotein (P-gp) substrates, which may decrease the clearance of drugs that are P-gp substrates. This P-gp interaction of neratinib would only be clinically relevant for P-gp substrate drugs with a narrow therapeutic window, such as digoxin. In a study with healthy subjects, neratinib was not associated with prolongation of the QTc interval at either the 240 mg daily dose of neratinib with food or under conditions of supratherapeutic plasma concentrations (neratinib 240 mg with ketoconazole 400 mg) (Neratinib IB).

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. Once-daily doses of lansoprazole, a PPI, administered with a single dose of neratinib to healthy subjects resulted in decrease of neratinib C_{max} by 71% and AUC by 65% compared with when neratinib was administered alone; there was a delay in t_{max} of 1.5 hours. The potential PK interaction of H2-receptor antagonists with neratinib has not been evaluated. It is unknown whether separating PPI or H2-receptor antagonist and neratinib doses reduce the interaction. If antacids are necessary, the antacid dose and the neratinib dose should be separated by 3 hours (Neratinib IB).

In clinical studies conducted in patients with advanced tumors who received neratinib 240 mg daily with weekly paclitaxel 80 mg/m^2, the PK data analysis suggested no meaningful differences in neratinib or paclitaxel exposure when administered as monotherapy compared with exposure when neratinib and paclitaxel were administered in combination (Study 3144A2-1115-JA and 3144A1-203-WW; Neratinib IB). In a clinical study conducted in women with advanced ERBB2-positive breast cancer who received neratinib 240 mg daily in combination with trastuzumab (a loading dose of 4 mg/kg, followed by 2 mg/kg weekly thereafter), the PK data analysis suggested no interactions between neratinib and trastuzumab (Study 3144A1-202-WW; Neratinib IB).

1.4. Adverse Event Profile of Neratinib Monotherapy

In neratinib monotherapy (240 mg/day) studies conducted in patients with early-stage HER2-positive, or locally advanced, or metastatic solid malignancies, the most frequently reported treatment-emergent adverse events (TEAEs) were associated with gastrointestinal disorders, and included diarrhea, nausea, abdominal pain, and vomiting (Neratinib IB).

In the Phase 3 Study 3144A2-3004-WW, in the extended adjuvant breast cancer setting, the intent-to-treat (ITT) population consisted of a total of 2840 subjects (1420 subjects in each arm) who had early stage HER2-positive breast cancer and had received prior adjuvant trastuzumab. The safety sample consisted of subjects who received at least 1 dose of study drug (neratinib or placebo), 1408 subjects in each arm. Subjects had a median age of 52 years (range, 23 to 83 years). Prophylactic loperamide was not mandated.

In the neratinib arm (N = 1408), Grade 3 TEAEs were reported for 684 (48.6%) patients and Grade 4 TEAEs for 15 (1.1%) patients. The most commonly reported Grade 3 TEAEs were diarrhea (561 subjects, 39.8%), vomiting (47 subjects, 3.3%), nausea (26 subjects, 1.8%), abdominal pain (24 subjects, 1.7%), and fatigue (23 subjects, 1.6%). The most common (>5%) adverse drug reactions (ADRs) occurring in patients receiving neratinib monotherapy are diarrhea, nausea, abdominal pain, abdominal pain upper, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, nail disorder, dry skin, abdominal distension, and urinary tract infection (see Neratinib IB).

In the placebo arm (N = 1408), Grade 3 TEAEs were reported for 169 (12.0%) patients and Grade 4 TEAEs for 14 (1.0%) patients. The most commonly reported Grade 3 TEAEs were diarrhea (23 subjects, 1.6%) and electrocardiogram QT prolonged (7 subjects, 0.5%).

During Study 3144A2-3004-WW, cardiac associated adverse events (AEs) were reported in 10.5% of subjects in the neratinib arm and 12.9% of subjects in the placebo arm. In contrast to treatment with other HER2-targeted agents, such as trastuzumab, 4 patients treated with neratinib reported nonserious Grade 3 AEs pertaining to left ventricular ejection fraction (LVEF). Three out of the 4 neratinib-treated patients had LVEF ≤50% that resolved after treatment interruption, and 1 patient had an absolute decrease of 9% from baseline of 54% to 45% that resolved after treatment discontinuation. One patient who discontinued due to LVEF decreased had comorbidities of Grade 1 diarrhea and Grade 3 hyperglycemia prior to the event.

Interstitial lung disease, which can sometimes be fatal, has been reported with other oral tyrosine kinase inhibitors that target EGFR and/or HER2, including lapatinib, gefitinib, and erlotinib. Rare cases of pneumonitis, which was considered to be drug related according to the Investigator's assessment, have been reported in clinical studies of neratinib. Patients receiving neratinib should be monitored for acute onset or worsening of pulmonary symptoms such as dyspnea, cough, and fever, and treated appropriately. Neratinib clinical safety data show no consistent pattern of hematologic toxicity and no biologic mechanism has been currently defined.

In Study 3144A2-3004-WW neratinib monotherapy arm, treatment-emergent serious adverse events (SAEs) that occurred in more than 4 patients were diarrhea (22 patients, 1.6%); vomiting (12 patients, 0.9%); dehydration (9 patients, 0.6%); cellulitis (6 patients, 0.4%); and erysipelas (5 patients, 0.4). Grade 4 ALT increased, and AST increased was reported for 3 (0.2%) patients each.

Refer to the most recent version of the IB for a summary of findings from nonclinical studies that potentially have clinical significance and from clinical studies that are relevant to the study (Neratinib IB). Also, refer to the IB for a summary of the known and potential risks and benefits to human patients.

1.5. Rationale for Proposed Combination Therapies with Neratinib in Select Cohorts

This open-label, multicenter, multinational, Phase 2 study has a basket design and as such it is predicated on the hypothesis that the presence of a molecular marker predicts response to the investigational products (Mandrekar et al, 2015).

In addition to the typical "basket" cohorts, identified mainly by mutation, this study includes cohorts recognizing the role of tumor histology, especially in the case of combination therapies. These cohorts are defined by tumor type and actionable mutations. The tumor type, the mutation and the combination therapy are identified prospectively, with patients assigned in a nonrandomized way to a specific treatment arm. As a result, the study is composed of multiple parallel "small' Phase 2 trials, with the cohorts defined by histology and mutations enrolling patients following a Simon's design based on response. During the conduct of the study, cohorts may be closed and new ones may be opened in new histologies, new molecular abnormalities and/or different treatment strategies may be examined based on data emerging from the trial itself, from other neratinib trials, or from clinical or preclinical data generated by the Sponsor or reported in literature.

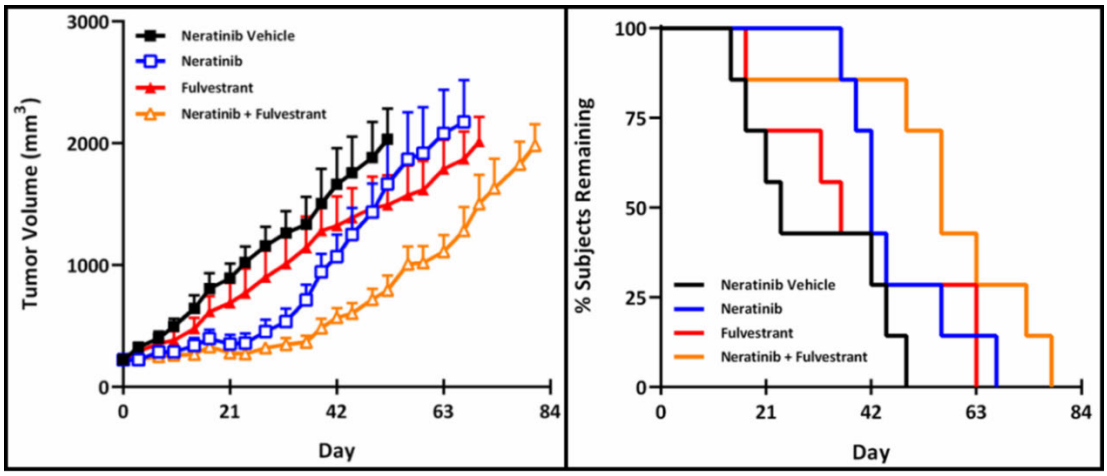
The following sections will discuss the rationale of patient selection on the basis of mutations and the rationale for the use of diverse therapeutic approaches in the different cohorts. Recent clinical studies have shown that dual inhibition of HER2, such as the combination of lapatinib and trastuzumab or trastuzumab and pertuzumab, is more effective than trastuzumab treatment alone (Baselga et al, 2012; Swain et al, 2013; Gianni et al, 2012). The rationale underlying the combination therapies in the lung, colon, and breast cancer cohorts is essentially to overcome the resistance due to oncogenic switches (Erjala et al, 2006) with dual ERBB blockade (neratinib and trastuzumab in lung, breast and colon cancer) or a blockade of a second oncogenic pathway (neratinib and fulvestrant in hormone receptor positive breast cancer). Notably, trastuzumab is effective in patients with advanced ERBB2-mutated lung cancer (Mazieres et al, 2016) and the combination of trastuzumab and lapatinib, another anti-EGFR TKI, was recently reported as effective in colorectal cancer (Siena et al, 2015). In addition, taxanes are extensively used with the anti-HER2 trastuzumab in breast cancer; clinical data suggest that their anticancer activity may be enhanced by ERBB mutations (Park et al, 2012).

1.5.1. Rationale for Treatment With Neratinib Combined With Fulvestrant in *HER2* Mutant Breast Cancer

The 'cross-talk' between the estrogen and HER*2* receptors has been previously reported, with *HER2* amplification resulting in reduced estrogen-receptor signaling (De Laurentiis et al, 2005; Dowsett et al, 2001). HER*2* overexpression increases the aggressiveness of breast cancer cells, lowering their response to endocrine therapies and resulting in a poorer prognosis. A review of patients with HER*2* overexpression who were treated with fulvestrant suggested these patients may receive benefit from dual HER*2*-ER targeting (Charif et al, 2014).

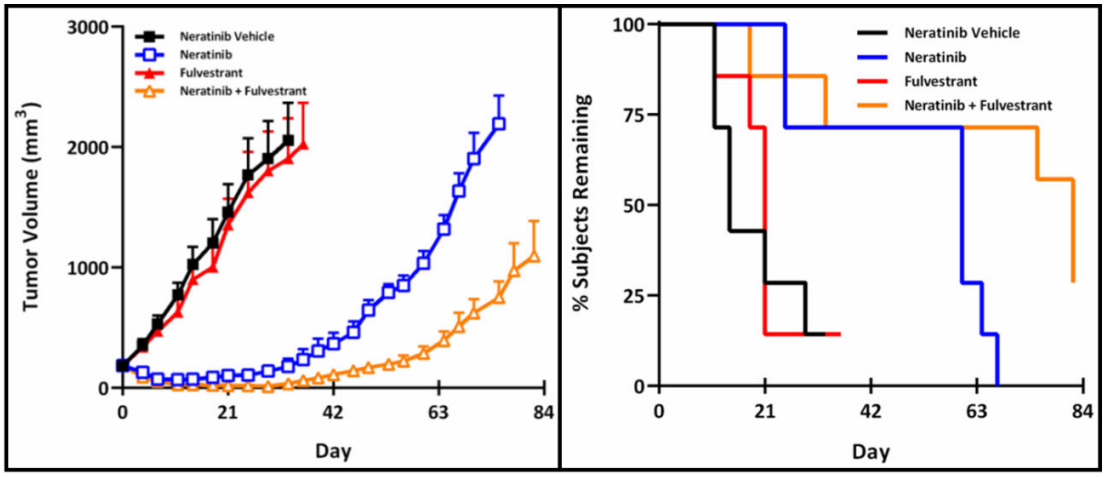
Endocrine responsiveness may also be limited by resistance potentially due to upregulation of HER*2*/*EGFR* signaling. Preclinical evidence suggests that combining fulvestrant and an *EGFR* blocker may be an effective anti-tumor strategy in HER*2*-overexpressing/positive cells (Emde et al, 2011). Therapies aimed at inhibiting the 'cross-talk' between ER and HER*2* using combinations of endocrine and HER*2*-directed therapies to overcome any potential ER signalling resistance mechanisms have been shown to improve anti-tumor efficacy compared to single agent treatments alone in preclinical studies. For example, in HER*2*+/ER+ breast cancer patient-derived xenograft (Figure 6) and cell-derived xenograft models (Figure 7), the combination of neratinib plus fulvestrant resulted in significant inhibition of tumor growth compared to single agent treatments (internal Puma data).

Figure 6: Neratinib Monotherapy or Neratinib Plus Fulvestrant Displays Enhanced Tumor Growth Inhibition in HER*2*+/ER+ Breast Patient-Derived Xenograft Model



Group	MTTE ± SD	T-C (Days)	*p-value	*Significant
Vehicle	24 ± 15	--	--	--
Neratinib	42 ± 11	18	0.0358	Y
Fulvestrant	36 ± 19	12	0.3803	N
Combination	60 ± 11	36	0.0009	Y
			[N]0.0266	Y
			[F]0.0188	[F]Y

Figure 7: Neratinib Monotherapy or Neratinib Plus Fulvestrant Displays Enhanced Tumor Growth Inhibition in Breast Cell-Derived Xenograft Model



Group	MTTE ± SD	T-C (Days)	p-value	Significant
Vehicle	14 ± 9	--	--	--
Neratinib	60 ± 3	46	<0.0001	Y
Fulvestrant	21 ± 7	7	0.6128	N
Combination	82 ± 3	68	<0.0001	Y
			[N]<0.0001	[N]Y
			[F]<0.0001	[F]Y

A retrospective chart analysis of 85 patients with metastatic breast cancer treated with fulvestrant with and without the HER*2* antibody treatment, trastuzumab, was recently conducted by Charif et al (2014); 13% of patients had documented HER*2*+ primary tumors that were treated with both fulvestrant and trastuzumab. The combination was associated with a longer clinical response (median duration of therapy 772 days [51-1911]) than HER*2* negative patients who received fulvestrant alone (median duration of therapy 360 days [60-2739]), suggesting that trastuzumab may help overcome resistance to fulvestrant (Charif et al, 2014).

1.5.1.1. Adverse Event Profile of Combination Therapy of Neratinib and Fulvestrant

Few clinical studies have explored the combination of fulvestrant with tyrosine kinase inhibitors in the clinical setting. Lapatinib was combined with fulvestrant in a randomized Phase 3 trial in patients with metastatic estrogen receptor (ER) positive, HER2+ breast cancer resistant to aromatase inhibitors (Burstein et al, 2014). The combination of fulvestrant plus lapatinib exhibited an overall response rate of 20% compared to 9% in the fulvestrant plus placebo arm alone. The combination regimen did not appear to decrease the tolerability of either agent alone. In the Phase 3 ExteNET study (NCT00878709), in a pre-specified subgroup analysis in the hormone receptor positive cohort in which >93% received concurrent hormone therapy, an enhanced neratinib benefit in improving disease free survival was observed (Chan et al, 2015). Diarrhea was the most common AE in neratinib-treated patients with 40% of patients reporting Grade 3 diarrhea (1 patient reported Grade 4 diarrhea). Other individual AEs ≥Grade 3 occurred in <4% of neratinib-treated patients. LVEF decrease ≥Grade 2 was seen in 1.3% of

neratinib-treated patients vs. 1.1% of placebo-treated patients. The mean relative dose intensity was 88% in neratinib-treated patients vs. 98% in placebo-treated patients.

As of the data cutoff date of 01-MAY-2017 for the Neratinib IB, there were 27 patients with *ERBB2* mutant breast cancer in the neratinib+fulvestrant combination therapy cohort of Study PUMA-NER-5201. At least 1 TEAE of Grade 1 to Grade 4 was reported for 25 (92.6%) patients. In this cohort, the most commonly reported (≥20% incidence) TEAEs of Grade 1 to 4 were: diarrhea (20 patients, 74.1%); nausea (10 patients, 37.0%); and constipation and decreased appetite (7 patients, 25.9%, each). Diarrhea was the only Grade 3 TEAE that occurred in more than 1 patient (3 patients, 11.1%). No TEAEs of Grade 4 or 5 were reported (Neratinib IB). No new safety signals from the neratinib+fulvestrant combination cohort have been observed.

Preclinical studies have shown that neratinib did not alter the mRNA or activity levels of any cytochrome P450 enzyme (CYP) studies at concentrations 7 times that of the 240 mg dose used in clinical trials. Based on these in vitro findings, it is improbable that neratinib will be involved in induction mediated drug-drug interactions with concomitant medications that are metabolized by CYP1A2, CYP2B6, CYP3A4 or CYP2C9. Given that fulvestrant is metabolized by CYP3A4, neratinib is unlikely to be involved in any drug-drug interactions with fulvestrant.

1.5.2. Rationale for Treatment With Neratinib Combined With Trastuzumab in *ERBB2* Mutant Breast Cancer

For HER*2*-positive breast cancer, there has been a focus in recent years to develop therapeutic agents to potentiate the effect of trastuzumab on target cells that have become resistant to trastuzumab. Preclinical evidence suggest that co-inhibition of HER*2*, other members of the HER family and/or the downstream pathway by giving trastuzumab/lapatinib in combination with other targeted therapies might prevent or at least prolong time to resistance and treatment failure (Baselga, 2010; O'Donovan et al, 2011).

There is clinical evidence that dual HER*2* blockade with trastuzumab in combination in women with metastatic HER*2*-positive breast cancer resulted in significant clinical benefit in a heavily pre-treated population (prior exposure to trastuzumab, lapatinib, T-DM1, a taxane, and multiple lines of chemotherapy; Jankowitz et al, 2013). Additionally in the clinic, lapatinib in combination with trastuzumab significantly improved overall survival and progression-free survival compared to lapatinib alone despite disease progression on prior trastuzumab-based therapy (Blackwell et al, 2010; Blackwell et al, 2012).

The combination of neratinib and trastuzumab had a greater growth inhibitory effect than either drug alone in both HER*2* over-expressing cell lines and cell lines that had acquired resistance to trastuzumab (Canonici et al, 2013; Figure 8). This result also held true in the mouse BT474 xenograft model. The xenograft experiment showed that the combination treatment lead to the greatest decrease in pHER2 with decreased activation of pAkt and pERK, correlating with increased efficacy compared to the single agents (Mazieres et al, 2016).

These examples support the notion that dual blockade using combination therapy is more effective than treatment with trastuzumab alone under conditions where HER*2* is over-expressed/amplified; the same approach may also work in a setting where *ERBB2* is mutated.

Figure 8: Combined Treatment With Neratinib and Trastuzumab Has an Additive Effect in Reducing BT474 and SKBR3 Cell Numbers

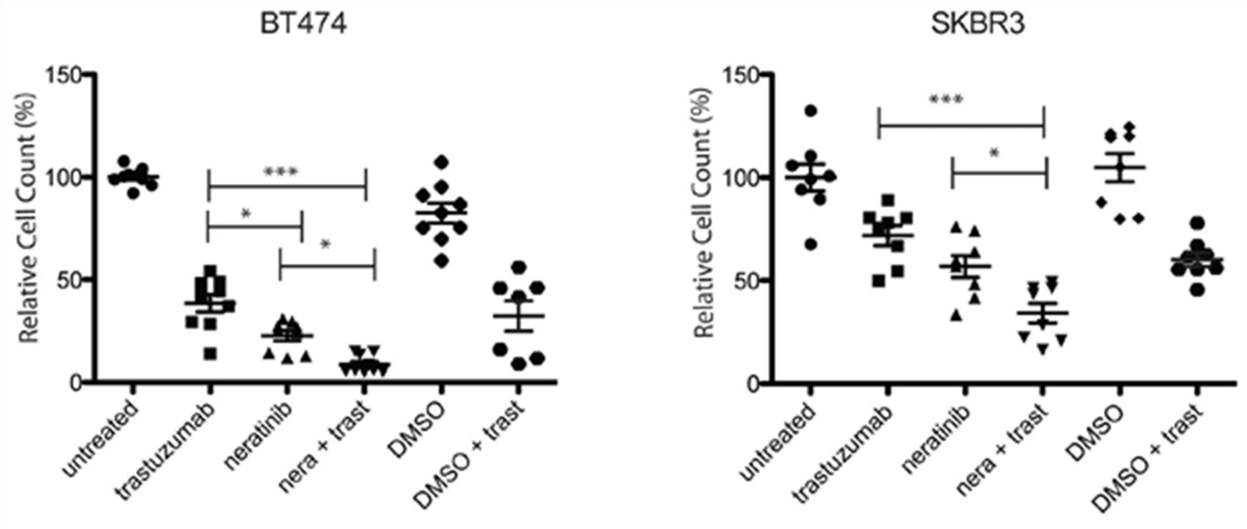


Table 1: Overall Response Rate (ORR), Disease Control (DC), Progression-free Survival (PFS, Weeks), and Overall Survival (OS, Weeks) According to Drug Type

Treatment	n	ORR	DC	PFS median (95% CI)	OS median (95% CI)
First-line; without *HER2*-targeting treatment	93	43.5%	70.7%	6 (5; 7.1)	24 (19.1; 36.4)
Second-line; without *HER2*-targeting treatment	52	10%	36%	4.3 (3.1; 5)	19.4 (9.6; 24.7)
EGFR-TKI[a]	26	7.6%	26.8%	2.99 (1.87; 4.47)	20.14 (7.14; 32.95)
Trastuzumab combination, T-DMI[a]	58	50.9%	75.5%	4.8 (3.4; 6.5)	13.3 (8.1; 15)
Neratinib, lapatinib, and afatinib[a]	29	7.4%	55.5%	3.4 (2.4; 4)	6.5 (4.7; 30.6)[a]

[a] If the same drug has been given more than one time, the results presented here are from their first administration.

1.5.3. Adverse Event Profile of Combination Therapy of Neratinib and Trastuzumab

Dual blockade with trastuzumab and neratinib was assessed in a Phase 1/2 clinical trial to determine the MTD and safety of the combination in patients with advanced breast cancer (Study 3144A1-202-WW, Neratinib IB). In Part 1 of the study, 4 patients received neratinib 160 mg and 4 patients received neratinib 240 mg in combination with trastuzumab 4 mg/kg as a loading dose and trastuzumab 2 mg/kg weekly thereafter. No dose limiting toxicity (DLT) was reported. In Part 2, all 37 patients received neratinib 240 mg in combination with trastuzumab 4 mg/kg as a loading dose and trastuzumab 2 mg/kg weekly thereafter. No MTD was defined for this study because no DLT was reported.

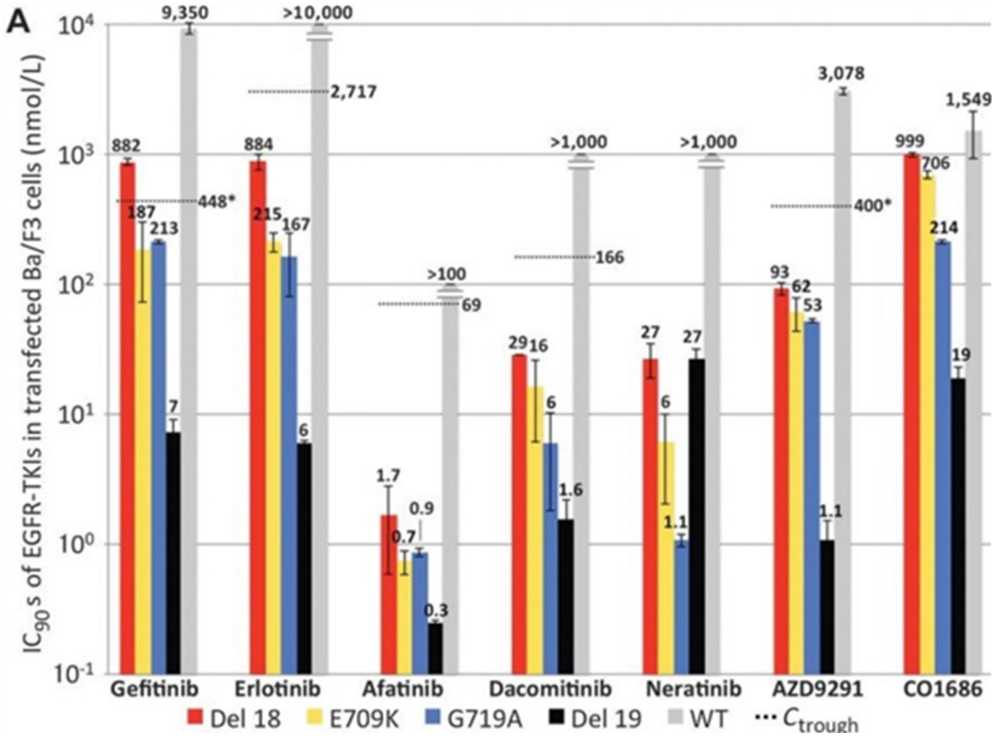
All 45 patients (100.0%) in the safety population reported at least 1 AE. The most commonly reported TEAEs of Grade 1 to 4 were diarrhea (42 patients, 93.3%), nausea (23 patients, 51.1%), decreased appetite (22 patients, 48.9%), vomiting (18 patients, 40.0%), and asthenia (13 patients, 28.9%). Grade 3 TEAEs that occurred in more than 1 patient were diarrhea (7 patients, 15.6%); and nausea, vomiting, AST increased, and dyspnea (2 patients, 4.4% each). Grade 4 TEAEs of metastases to the central nervous system and hyperbilirubinemia were reported for 1 patient each. Grade 5 TEAE of disease progression was reported for 1 patient.

Based on the above safety data and the low risk of drug-drug interactions with the combination of trastuzumab and neratinib, the risk of additional toxicities using a single 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks is small.

1.6. Rationale for Treatment with Neratinib Monotherapy in *EGFR* Exon 18 Mutant Lung Cancer

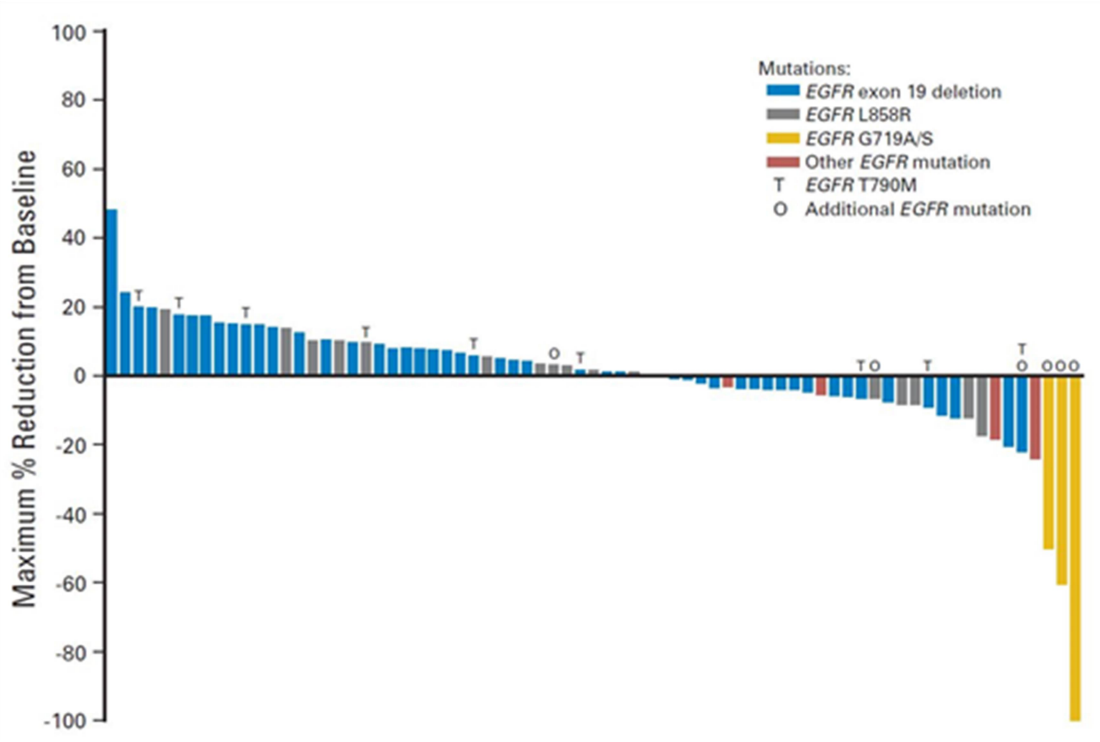
In a preclinical study, NIH-3T3 cells transfected with EGFR exon 18 mutations (Del18, E709K, and G719A) were observed to form foci with marked pile-up (Kobayashi et al, 2015). This indicated that EGFR Del18, E709K, and G719A were oncogenic drivers. Furthermore, Ba/F3 cells transfected with EGFR exon 18 mutations (Del18, E709K, and G719A) exhibited higher sensitivity to neratinib (25-fold for G719A, 5-fold for E709K, and by comparable extent for Del18) compared to control cells (Kobayashi et al, 2015). Compared with various EGFR tyrosine kinase inhibitors, including irreversible pan-HER TKIs (eg, afatinib), neratinib demonstrated the most sensitivity for blocking cell proliferation in exon 18 mutant Ba/F3 cells in vitro (Figure 9; Kobayashi et al 2015).

Figure 9: Sensitivity of Ba/F3 Cells Expressing Exon 18 Mutations to Various EGFR Tyrosine Kinase Inhibitors



In a Phase 2 trial of neratinib in patients with advanced NSCLC who previously benefited from first-generation TKI and developed acquired resistance, it was ascertained that a response to neratinib was observed in patients harboring the *EGFR* exon 18 G719X point mutation (Sequist et al, 2010; Figure 10). Three of the 4 patients harboring G719X mutations had a partial response and the fourth had SD that lasted for 40 weeks (PFS: 52.7 weeks, 90% CI: 25.6 to 57 weeks). It was noted that one of the patients who demonstrated a partial response and the patient with SD had transitioned from receiving erlotinib (due to lack of treatment response) to neratinib.

Figure 10: Percent Change in Measurable Tumor for *EGFR* Mutation-Positive NSCLC Patients Treated with Neratinib



More recently, the incidence and natural epidemiology of lung cancer patients with tumors harboring *EGFR* exon 18 mutations were reviewed at Memorial Sloan Kettering Cancer Center to better understand the clinical-pathological characteristics and outcomes to TKI therapy (Lai et al, 2017). Patients with *EGFR* exon 18 mutations appeared to have a shorter median overall survival (OS; 22 months vs. 31 months) when compared to patients with more common sensitizing *EGFR* mutations (Lai et al, 2017).

The above preclinical and clinical results suggest that NSCLC patients with tumors harboring *EGFR* exon 18 mutations may benefit with neratinib monotherapy. Part of the primary objective of this study will be to determine whether neratinib monotherapy induces tumor regression in NSCLC patients with tumors harboring *EGFR* exon 18 mutations.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of this study, applicable to each cohort, are:

For the randomized hormone receptor positive (HR+), *HER2* negative metastatic breast cancer:

- To determine the confirmed objective response rate (ORR) by independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

For the metastatic cervical cancer cohort:

- To determine the confirmed ORR by independent central review according to RECIST v1.1

For all other cohorts:

- To determine the first objective response rate (ORR_{first}) by investigator at the first post-baseline tumor assessment

2.2. Secondary Objectives

The secondary objectives of this study, applicable to each cohort, are:

For the randomized hormone receptor positive (HR+), *HER2* negative metastatic breast cancer:

- To determine the confirmed ORR by investigator
- To determine the duration of response (DOR) by both independent central review and investigator
- To determine the clinical benefit rate (CBR) by both independent central review and investigator
- To determine the progression-free survival (PFS) by both independent central review and investigator

For the metastatic cervical cancer cohort:

- To determine the confirmed ORR by investigator
- To determine the DOR by both independent central review and investigator
- To determine the CBR by both independent central review and investigator
- To determine the PFS by both independent central review and investigator
- To determine overall survival (OS)

For all other cohorts:

- To determine the confirmed ORR by investigator
- To determine the DOR by investigator

- To determine the CBR by investigator
- To determine the PFS by investigator
- To determine OS

For all cohorts including the randomized HR+, *HER2* negative metastatic breast cancer and metastatic cervical cancer cohorts, the safety objectives are:

- To assess the safety profile and tolerability of study treatments
- To assess Patient Reported Outcomes (PRO)

2.3. Exploratory Objectives

For all cohorts including the randomized HR+, *HER2* negative metastatic breast cancer and metastatic cervical cancer cohorts, the exploratory objectives are:

- To collect and retrospectively evaluate somatic mutations or gene aberrations using next-generation sequencing (NGS) in the most recent pretreatment tumor biopsy or fresh tumor tissue biopsies at a central laboratory.
- To explore genetic modifiers of sensitivity and/or resistance to neratinib using molecular profiling techniques in pretreatment archival and/or fresh tumor specimens and paired normal whole blood.
- To evaluate cell-free DNA (cfDNA) from plasma specimens collected at baseline/screening, during the course of treatment, and upon disease progression to identify *HER2* and *EGFR* mutations and other gene aberrations and to assess any potential associations with neratinib sensitivity and/or primary/acquired resistance to neratinib or neratinib-containing therapy.
- To evaluate potential genes or protein biomarkers that may be reported to confer neratinib sensitivity and/or primary/acquired resistance to neratinib or neratinib-containing therapy from *optional* fresh core tumor biopsies during time of treatment and/or at the time of treatment discontinuation or disease progression.

3. OVERALL DESIGN AND PLAN OF THE STUDY

3.1. Study Design

This is an open-label, multicenter, multinational, Phase 2 study exploring the efficacy and safety of neratinib as monotherapy or in combination with other therapies in patients with *HER* (*EGFR*, *HER2*) mutation-positive solid tumors. Patients with tumors harboring somatic mutations in *HER* will be identified through previously documented mutation testing performed prior to screening. The presence of human *HER* mutations (*EGFR*, *HER2*) will be retrospectively confirmed by central testing NGS sequencing. The study has a basket design and includes several cohorts, either defined by an actionable somatic mutation or by actionable mutation and tumor histology (for example *HER2* mutant cervical cancer). In the course of the study, enrollment in certain cohorts can be completed and enrollment in new cohorts initiated to test the anticancer effect of neratinib in other histologies, specific molecular abnormalities and/or in combination with other drugs.

Patients with *HER2* mutant, *HER2* negative breast cancer will be divided into different treatment cohorts on the basis of HR status: HR negative (Triple Negative Breast Cancer [TNBC]) and HR+.

- Patients in the HR negative cohort (TNBC) will receive neratinib in combination with trastuzumab (Table 3).
- Patients in the HR+, *HER2* negative, *HER2* mutant breast cancer cohort with RECIST measurable tumors and who have been previously treated with CDK4/6 inhibitors (CDK4/6i) will be randomized to receive single agent fulvestrant, fulvestrant in combination with trastuzumab, or neratinib in combination with trastuzumab and fulvestrant with a randomization ratio of 1:1:1. Randomization will be stratified by the number of lines of prior therapy for metastatic disease (≤ 2 and >2 lines) and prior fulvestrant therapy (Table 2).
- The randomized HR-positive (HR +), *HER2* negative, *HER2* mutant metastatic breast cancer cohort is designed to investigate the individual contribution of neratinib and/or trastuzumab to fulvestrant via Simon's 2 stage optimal design. The decision to carry over on enrollment of each arm in the cohort will be based on stage I and II analysis of Simon's 2 stage in consultation with the Independent Data Monitoring Committee (IDMC).
  - Patients in the HR+ cohort who receive single agent fulvestrant or fulvestrant plus trastuzumab will be eligible for triplet therapy (neratinib, fulvestrant, trastuzumab) upon progression. Patients who have unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease related symptoms before the first scan post-treatment are eligible for the triplet therapy. Efficacy will be determined based on response to initial regimen only.
- Patients in the HR+ cohort who have not received prior CDK4/6i therapy (eg. CDK4/6i naïve) will receive neratinib in combination with trastuzumab and fulvestrant as part of an open label cohort (Table 3).

The cervical cancer cohort and cohorts not receiving trastuzumab are summarized in Table 4 and Table 5, respectively.

The trial will consist of a screening period, a treatment period, and a follow-up period after the study therapy is discontinued for any reason. An end of treatment (EOT) assessment is performed 28 days (+14 days) after the last dose of investigational product(s) and adverse events are collected 28 days after the last dose of investigational product(s).

Neratinib will be administered orally with food once daily (recommended to be taken in the morning), on a continuous basis. Dose delays and modifications will be handled as per instructions in the package insert. All patients taking neratinib will maintain a patient diary for the study to record each dose of neratinib taken and while receiving antidiarrheal prophylaxis with loperamide taken for the first two cycles of treatment. For cohorts receiving combination treatment that includes trastuzumab, post-treatment radiographic evaluation of their disease will be conducted every 3 cycles. For all other cohorts, post-treatment disease assessment will be conducted every 2 cycles. Treatment should be administered until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms. Tumor markers or circulating tumor cells should not be used as the sole criteria for determining progression. At the time of decision regarding disease progression, radiological exam should be performed. Patients will continue on study treatment until disease progression, unacceptable toxicity, patient withdrawal of consent, or death. Patients who develop disease progression, but in the opinion of the Investigator would still benefit from continuing study, may continue on per-protocol therapy if approved by the Sponsor. Survival follow-up will be every 12 weeks after treatment discontinuation. Enrollment will continue as dictated by the Simon's 2-stage design in all the histology and mutation specific cohorts and/or up to 30 patients per cohort in multi-cancer, mutation specific NOS cohorts. Enrollment in the randomized breast cancer, non-randomized breast cancer and cervical cancer cohorts will also continue as dictated by the Simon's 2-stage design up to 50 patients per cohort.

Table 2: Randomized Breast Cancer Cohort

Tumor Cohort	Mutation	Randomized Treatment	Sample Size (# subjects)
Breast HR Positive (with prior CDK4/6i)	*HER2* mutant	• Fulvestrant: 500 mg IM on Study Day 1, 15, and 29; once every 28 days thereafter Or • Fulvestrant: 500 mg IM on Study Day 1, 15, and 29; once every 28 days thereafter • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks Or • Neratinib: 240 mg PO daily • Fulvestrant: 500 mg IM on Study Day 1, 15, and 29; once every 28 days thereafter • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks	Up to 18 Up to 18 Up to 50

Table 3: Non-randomized Breast Cancer Cohorts

Tumor Cohort	Mutation	Assigned Treatment	Cohort Sample Size (# subjects)
Breast HR Positive (CDK4/6i naïve)	*HER2* mutant	• Neratinib: 240 mg PO daily • Fulvestrant: 500 mg IM on Study Day 1, 15, and 29; once every 28 days thereafter • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks	Up to 50
Breast TNBC (HR Negative)	*HER2* mutant	• Neratinib: 240 mg PO daily • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks	Up to 50

Table 4: Cervical Cancer Cohort

Tumor Cohort	Mutation	Assigned Treatment	Cohort Sample Size (# subjects)
Cervical	*HER2* mutant	• Neratinib: 240 mg PO daily	50

Table 5: Cohorts Not Receiving Trastuzumab

Tumor Cohort	Mutation	Assigned Treatment
Salivary Gland	*HER2* mutant	• Neratinib: 240 mg PO daily
Non-small Cell Lung	*EGFR* exon 18 mutations	• Neratinib: 240 mg PO daily

Tumor Cohorts Closed to Enrollment in Amendment 7

The following cohorts were closed to enrollment in Amendment 7: solid tumors (NOS) *HER2* mutant treated with neratinib monotherapy and *HER2* mutant bladder/urinary tract cancer treated with neratinib + paclitaxel.

The approximate duration of the study is 90 months and approximate duration for patient's participation is 18 months.

The end-of-study (EOS) is defined as the last visit of the last patient or the completion of any/all follow-up monitoring and data collection described in the protocol (ie, survival).

The EOS will occur when all patients have been followed for OS or death, withdrawal of consent, or are lost to follow-up. The Sponsor reserves the right to terminate the study early for any reason and offer patients receiving treatment benefit the option to continue to receive neratinib via a separate treatment extension study or an expanded access protocol.

3.2. Randomization and Blinding

Patients in the HER2-negative, *HER2* mutant, HR positive breast cancer cohort with RECIST measurable tumors who have previously been treated with CDK4/6 inhibitors (CDK4/6i) will be randomized to receive single agent fulvestrant, fulvestrant in combination with trastuzumab, or neratinib in combination with trastuzumab and fulvestrant with a randomization ratio of 1:1:1. Randomization will be stratified by the number of lines of prior therapy for metastatic disease (≤ 2 and >2 lines) and by prior exposure to fulvestrant.

Randomization will be suspended after the 21st patient unless the decision has been made previously to drop any cohort earlier for futility/safety, and further patients will be enrolled into the T+N+F arm until the 'final' decision on expansion into the second stage has been made, randomization has been reintroduced (if 2 or 3 cohorts remain) or sufficient data are present to reconvene with the Independent Data Monitoring Committee (IDMC).

For all other cohorts, this is an open-label, single arm study.

4. STUDY POPULATION

4.1. Inclusion Criteria

Each patient will be entered into this study only if she/he meets all of these criteria:

1. Men and women who are ≥18 years old at signing of informed consent.
2. At the time of screening, histologically confirmed cancers in patients with previously documented activating *EGFR (exon 18)* or qualifying *HER2* mutation confirmed by a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalent laboratory, and who are refractory to standard therapy or for which standard or curative therapy does not exist or is not considered sufficient or appropriate.
3. At least one measurable lesion, as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1; Eisenhauer et al, 2009).
4. Left ventricular ejection fraction (LVEF) ≥50% measured by multiple-gated acquisition scan (MUGA) or echocardiogram (ECHO).
5. Eastern Cooperative Oncology Group (ECOG) status of 0 to 2.
6. Female patients with cancers known to secrete β-human chorionic gonadotropin (hCG), ie germinomas, are eligible if the pattern of serum β-hCG is suggestive of the malignancy and the pelvic ultrasound is negative for pregnancy.
7. Male patients must agree and commit to use a barrier method of contraception while on treatment and for 3 months after the last dose of trastuzumab, fulvestrant, or neratinib monotherapy. Patients of child-bearing potential must agree and commit to the use of a highly effective double-barrier method of contraception (eg, a combination of male condom with an intravaginal device such as the cervical cap, diaphragm, or vaginal sponge with spermicide) or a non-hormonal method, from the signing of the informed consent until:
    i. 28 days after the last dose of neratinib monotherapy, or
    ii. 7 months after last dose of trastuzumab or
    iii. 1 year after the last dose of fulvestrant.
8. Provide written, informed consent to participate in the study and follow the study procedures.
9. Agree to provide most recent metastatic tumor sample or fresh tumor biopsy, and plasma/blood specimens for gene sequencing and other biomarker analysis.

<u>Additional Inclusion Criteria for all Breast Cancer Patients that Harbor *HER2* Mutations and NCSLC Patients that Harbor *EGFR* exon 18 Mutations</u>

10. Must provide a pretreatment fresh biopsy within 28 days prior to starting treatment unless the biopsy procedure presents a safety concern for the patient as determined by the Investigator, or other exceptional reason upon agreement with the Sponsor

Additional Inclusion Criteria for HR+ Breast Cancer Patients with Tumors that Harbor *HER2* Mutations

11. HR+ disease defined as ≥1% estrogen receptor (ER) positive and/or progesterone receptor (PR) positive cells (performed on the most recent biopsy as assessed locally and consistent with current American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) or European Society of Medical Oncology (ESMO) guidelines):
12. Biopsy from a non-bony metastatic site: preferred, or
    a. Biopsy from bony metastasis or if the sample is considered inadequate or unavailable: assessment of HR status will be at the Investigator's discretion.
13. Postmenopausal, as defined by at least one of the following criteria:
    a. Age ≥60 years;
    b. Age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and serum estradiol and follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females;
    c. Documented bilateral oophorectomy,
14. Medically confirmed ovarian failure

    OR
15. Pre/perimenopausal, ie, not meeting the criteria for being postmenopausal:
    a. Pre/perimenopausal women can be enrolled if amenable to be treated with a luteinizing hormone receptor hormone (LHRH) agonist. Patients must have commenced treatment with an LHRH agonist at least 4 weeks prior to the first dose of neratinib.
16. Prior treatment with chemotherapy or hormonal therapy (including fulvestrant).

4.2. Exclusion Criteria

A patient will be excluded from this study if she/he meets any of these criteria:

1. Patients harboring ineligible somatic *HER2* mutations, such as those that are subclonal in nature or those resulting in the expression of truncated proteins including alterations that result in premature stop codon or a change in reading frame (ie, frame shift mutations).
2. Prior treatment with any pan-*HER*-, *HER2*-, or *EGFR* tyrosine kinase inhibitor (TKI) (eg, lapatinib, afatinib, dacomitinib, neratinib, tucatinib, poziotinib, gefitinib, erlotinib, osimertinib) is excluded with the following exception: patients with *EGFR* exon 18 mutated NSCLC who may have received afatinib, osimertinib, or other pan-*HER* or *EGFR* TKIs remain eligible.
3. Not recovered to at least Grade 1 at screening (Common Terminology Criteria for Adverse Events v4.0 [CTCAE v4.0]) from all clinically significant adverse events related to prior therapies (excluding alopecia).

4. Received chemotherapy or biologic therapy ≤2 weeks or 5 half-lives ($t_{½}$) of the agent used, whichever is shorter, prior to the initiation of investigational product.
5. Received radiation therapy ≤14 days prior to initiation of investigational product.
6. Patients who are receiving any other anticancer agents with the exception of patients on 1) a stable dose of bisphosphonates or denosumab or 2) sex hormone therapy in the case of breast, or gynecological cancers.
7. Received prior therapy resulting in a cumulative epirubicin dose >900 mg/m^2 or cumulative doxorubicin dose >450 mg/m^2. If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 450 mg/m^2 doxorubicin.
8. Symptomatic or unstable brain metastases. (Note: Asymptomatic patients with metastatic brain disease who have been on a stable dose of corticosteroids for at least 14 days are eligible to participate in the study.)
9. Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2), unstable angina (symptomatic angina pectoris within the past 180 days that required the initiation of or increase in anti-anginal medication or other intervention), myocardial infarction within 12 months of enrollment, or ventricular arrhythmia (except for benign premature ventricular contractions).
10. Demonstrates a QTc interval >450 ms for men or >470 ms for women or known history of congenital QT-prolongation or Torsade de pointes (TdP).
11. Inadequate bone marrow, renal or hepatic function as defined on screening laboratory assessments outside the following limits:

Laboratory Assessments Endpoints

Laboratory endpoint	**Required limit for exclusion**
Absolute neutrophil count (ANC)	<1,000/µL (1.0 x 10^9 /L)
Platelet count	<100,000/µL (<100 x 10^9/L)
Hemoglobin	<8 g/dL (transfusion allowed to treat low hemoglobin) Transfusion must be at least 7 days prior to C1D1.
Total bilirubin	>1.5 x institutional upper limit of normal (ULN) (in case of known Gilbert's syndrome, >2x ULN)
Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)	>3 x institutional ULN OR >5 x ULN if liver metastases are present

Laboratory endpoint	Required limit for exclusion
Creatinine	>1.5 x institutional ULN OR Calculated Creatinine Clearance <30 mL/min (as measured directly with a 24-hour urine or calculated by Cockcroft-Gault formula [a] or Modification of Diet in Renal Disease [MDRD] formula [b])

[a] Cockcroft and Gault, 1976.

[b] Levey et al, 1999.

12. Active infection or unexplained fever >38.5°C (101.3°F).
13. Women who are pregnant, are planning on becoming pregnant, or are breast-feeding.
14. Significant chronic gastrointestinal disorder with diarrhea as a major symptom (eg, Crohn's disease, malabsorption, or Grade ≥2 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE version 4.0] diarrhea of any etiology at baseline).
15. Clinically active infection with a hepatitis virus.
16. Evidence of significant medical illness, abnormal laboratory finding, or psychiatric illness/social situations that could, in the Investigator's judgment, make the patient inappropriate for this study.
17. Known hypersensitivity to any component of the investigational product, required combination therapy, or loperamide.
18. Unable or unwilling to swallow tablets.
19. Patients with known activating *KRAS* mutations.

Additional Exclusion Criteria for Patients with Breast Cancer With *HER2* Mutations

20. Patients with known *HER2*+ tumors (protein overexpression or gene amplification as defined by ASCO/CAP guidelines or HER2 amplifications as determined by copy number alterations by NGS) are excluded.

Additional Exclusion Criteria for Patients With *HER2* Mutations Treated With Trastuzumab Combination Therapy or Being Randomized into HR+ Breast Cancer Cohorts

21. Hypersensitivity to trastuzumab, murine proteins or any of the excipients listed in the Herceptin label.
22. Severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

4.3. Patient Enrollment

Enrollment will occur only after the patient has given written informed consent, all screening assessments have been completed, and the patient meets all eligibility criteria.

4.4. Cohort Assignment

Patients will be assigned to cohorts based on tumors harboring somatic mutations in *EGFR* or *HER2* identified through previously documented mutation testing performed prior to screening and by the tumor type and approved by the Sponsor (Appendix 7).

Mutation status of a tumor should be documented using molecular assays available at study sites (Appendix 7).

5. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

5.1. Investigational Product Administration

The investigational product administration schedule is outlined in Table 6, and is described in the subsections below. For patients enrolled to a *HER2*-mutant bladder cohort treated with neratinib in combination with paclitaxel reference Protocol Amendment 6/6.1 for paclitaxel investigational product administration details.

Table 6: Investigational Product Administration Schedule

Study Drug	Total Initial Dose	Administration	Dosing Schedule
Neratinib	240 mg	Oral (PO) 6 x 40 mg tablets	Daily, continuously
Fulvestrant[a]	500 mg	IM 2 x 250 mg injections	Days 1, 15, and 29; then once every 4 weeks thereafter; see Schedule of Procedures, Appendix 1 Table A1.1 and Table A1.2.
Trastuzumab[b]	8 mg/kg on C1D1, then 6 mg/kg	IV	C1D1 then once every 3 weeks thereafter; see Schedule of Procedures, Appendix 1 Table A1.1.

[a] Dosing schedule will include a window of ±2 days. For dosing outside the window, the Medical Monitor needs to be informed. For rate of administration, premedication, treatment of infusion reactions, and for dose adjustments, consult the label of fulvestrant . For patients with hepatic impairment defined by the Childs-Turcott-Pugh Class B criteria, the dose of fulvestrant should be reduced to 250 mg as one 5 mL injection on the same schedule.

[b] Dosing schedule will include a window of ±7 days. For dosing outside the window, the Medical Monitor needs to be informed. If rounding is necessary, trastuzumab should be rounded to the nearest 20 mg. Infusion of trastuzumab should be performed in accordance with local guidelines and/or prescribing information, consult the label of trastuzumab.

5.1.1. Neratinib

Neratinib is self-administered as six 40-mg tablets (total daily dose 240 mg) orally, once daily with food (recommended to be taken in the morning), continuously.

Daily dosing should continue until a criterion for treatment withdrawal is met (see Section 9.1).

5.1.2. Fulvestrant

Patients receiving fulvestrant (see Table 2) will receive 500 mg total dose of fulvestrant administered as two 5 mL intramuscular (IM) injections, one in each buttock, on Day 1, 15, and 29; then once every 4 weeks thereafter (Appendix 1 Table A1.1 and Table A1.2). For patients with hepatic impairment defined by the Childs-Turcott-Pugh Class B criteria, the dose of fulvestrant should be reduced to 250 mg as one 5 mL injection on the same schedule.

Dosing should continue until a criterion for treatment withdrawal is met (see Section 9.1).

5.1.3. Trastuzumab

Patients receiving trastuzumab combination therapy (see Table 2) will receive an initial dose of 8 mg/kg of trastuzumab IV administered on C1D1, followed by 6 mg/kg IV once every 3 weeks thereafter (Appendix 1 Table A1.1 and Table A1.2).

Trastuzumab infusion should be interrupted in all patients experiencing significant signs/symptoms, and intervention of medical therapy should be administered, which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions (follow Herceptin [trastuzumab] package insert).

Dosing should continue until a criterion for treatment withdrawal is met (see Section 9.1).

5.2. Investigational Product Dose Adjustment for Toxicity

Dose adjustment and/or discontinuation for fulvestrantand trastuzumab should follow dosing guidelines provided in Section 5.3.1 through Section 5.3.3 and the respective country-approved label. If, in the opinion of the investigator, the patient will be discontinued from combination therapy with fulvestrant or trastuzumab but may benefit from neratinib single agent, patient may remain on study after consulting the medical monitor.

Recommended dose reductions for the -1 and -2 dose levels are listed in Table 7.

Table 7: Dose Reduction Levels for Investigational Product-Related Toxicity

Study Drug	Initial Dose	Dose Level -1	Dose Level -2
Neratinib	240 mg	160 mg	120 mg
Fulvestrant	500 mg	250 mg	NA
Trastuzumab	8 mg/kg for Cycle 1 and then 6 mg/kg for the remaining cycles	NA	NA

If doses of the IPs are held, study procedures for that cycle will proceed on schedule as planned, without any delay. This also applies to tumor assessments, which should continue as per cohort schedule regardless of any changes in dose or occurrence of AEs. Missed dose(s) of IPs (ie, any dose that is not administered within the protocol-defined administration window; Table 6) will not be made up. **Note: Patients should take one dose of neratinib per calendar day.**

The dose adjustment guidelines represent the minimum set of measures the Investigator 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. If other toxicities are observed, consult the approved country label and the medical monitor.

Once a 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 will only be permitted if explicitly approved in advance by the Sponsor. Evidence of this approval must be contained within the patient's source file.

Patients should discontinue IP if a criterion for withdrawal is met (see Section 9.1).

Detailed rules for dose adjustments of IP in case of toxicity, including the dose levels to which IP should be adjusted, are provided in Table 8 to Table 15.

For infusion reactions requiring dose adjustment, follow the country-approved label for trastuzumab as appropriate.

Table 8: General Toxicity Related to Neratinib and Requiring Dose Adjustment[a]

NCI CTCAE v.4.0[b]	Action with Neratinib
Grade 2 adverse reaction	
• 1st appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume neratinib at the starting dose level.
• 2nd appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg.
• 3rd appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg.
• 4th appearance	• Discontinue **neratinib** permanently.
Grade 3 adverse reaction	
• 1st appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg.
• 2nd appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg.
• 3rd appearance	• Discontinue **neratinib** permanently.
Grade 4 adverse reaction	
• 1st appearance	• Discontinue **neratinib** permanently OR if Investigator deems it to be in the patient's best interest to continue, hold **neratinib** until resolved to Grade ≤1; then resume **neratinib** at 160 mg. • If the event occurs again despite one dose reduction, permanently discontinued **neratinib.**

[a] For fulvestrant and trastuzumab, follow the country-approved label.
[b] Based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

Table 9: Diarrhea Related to Neratinib and Requiring Dose Adjustment

NCI CTCAE V4.0	Action with Neratinib
Grade 1 Diarrhea [Increase of <4 stools per day **over baseline**; mild increase in ostomy output compared to baseline.] OR **Grade 2 Diarrhea** [Increase of 4-6 stools per day **over baseline**; moderate increase in ostomy output compared to baseline;] lasting <5 days OR **Grade 3 Diarrhea** [Increase of ≥7 stools per day **over baseline**; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline limiting self-care activities of daily living (ADL)] **lasting <2 days**	• Adjust anti-diarrheal treatment, as per the guidelines for management of diarrhea at the first onset of diarrhea. Continue **neratinib** at full dose. (see Section 6.1.2.1) • Instruct patient to follow dietetic recommendations in the guidelines for management of diarrhea (see Section 6.1.2.1 for dietetic measures) • Fluid intake of ~2L should be maintained to avoid dehydration. • Once the event resolved to ≤ Grade 1 or baseline, continue loperamide as per the guidelines for management of diarrhea at the first onset of diarrhea. Continue **neratinib** at full dose. (see Section 6.1.1)

Persisting and intolerable **Grade 2 Diarrhea** lasting >5 days despite being treated with optimal medical therapy, or associated with fever, dehydration, or **Grade 3-4 neutropenia**
OR
Grade 3 Diarrhea lasting > 2 days despite being treated with optimal medical therapy, or associated with fever, dehydration, or **Grade 3-4 neutropenia**
	• Adjust anti-diarrheal treatment, as per the guidelines for management of diarrhea at the first onset of diarrhea. (see Section 6.1.2.1 pharmacological treatment)
	• Hold **neratinib** until recovery to ≤ Grade 1 or baseline.
	• Instruct patient to follow dietetic recommendations of the guidelines for management of diarrhea (see Section 6.1.2.1 for dietetic measures)
	• Fluid intake of ~2L should be maintained, intravenously if needed.
	• If diarrhea resolves to Grade 0-1:
	  • ≤1 week after withholding treatment, resume same dose of neratinib.
	  • Within 1-4 weeks after withholding treatment, reduce neratinib dose to the next lower dose level.
	  • If event occurs a 2nd time and the **neratinib** dose has not already been decreased, reduce **neratinib** dose to the next lower dose level.
	  • If subsequent events occur, reduce **neratinib** dose to the next lower dose level.
	  • Once the event resolved to ≤Grade 1 or baseline, start loperamide 4 mg with each subsequent **neratinib** administration.

Any Grade 4 diarrhea [Life-threatening consequences; urgent intervention indicated]	• Permanently discontinue **neratinib**

Table 10: Pulmonary Toxicity Related to Neratinib or Trastuzumab Requiring Dose Adjustment

NCI CTCAE V4.0	Action with Neratinib	Action with Trastuzumab
Grade 2 Pneumonitis/Interstitial Lung Disease [Symptomatic; medical intervention indicated; limiting instrumental ADL]	• Hold **neratinib** until recovery to ≤ Grade 1 or baseline. • Reduce **neratinib** to 160 mg or discontinue **neratinib** as per Investigator's best medical judgment.	• Hold **trastuzumab** until recovery to ≤ Grade 1 or baseline; then resume dosing.
Grade ≥3 Pneumonitis/Interstitial Lung Disease [Severe symptoms; limiting self-care ADL; oxygen indicated]	• Discontinue **neratinib** permanently	• Discontinue **trastuzumab** permanently.

Table 11: Dose Adjustment for Neratinib or Fulvestrant for Patients With Hepatic Impairment

LIVER FUNCTION TOXICITY	Action with Neratinib	Action with Fulvestrant
Childs-Turcott-Pugh Class A	• No dose adjustment required.	• Continue 500 mg
Childs-Turcott-Pugh Class B	• No dose adjustment required.	• Reduce dose to 250 mg on same schedule of administration
Childs-Turcott-Pugh Class C	• Reduce starting dose to 80 mg in patients with severe hepatic impairment	• No data in this patient population; consult with medical monitor

Table 12: Liver Toxicity Requiring Dose Adjustment

NCI CTCAE V4.0	Action with Neratinib	Action with Fulvestrant	Action with Trastuzumab
Grade 3 ALT/AST (>5-20x ULN) **OR Grade 3 bilirubin** (>3-10x ULN)	• Hold **neratinib** until recovery to ≤ Grade 1 for patients with ALT/AST ≤ Grade 1 at baseline OR ≤ Grade 2 for patients with Grade 2 ALT/AST at baseline. • Evaluate alternative causes. • For patients with ALT/AST ≤ 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, AST or bilirubin occurs again despite one dose reduction, permanently discontinue **neratinib**. For patients with Grade 2 ALT/AST at baseline due to liver metastases: contact the Sponsor for guidance on appropriate dose adjustments.	Refer to Table 11.	• No dose adjustment required
Grade 4 ALT/AST (>20x ULN) OR **Grade 4 Bilirubin** (>10x ULN)	• Permanently discontinue neratinib. • Evaluate alternative causes.	• Permanently discontinue • Evaluate alternative causes	• Permanently discontinue • Evaluate alternative causes
ALT/AST >3x ULN AND **Total bilirubin** >2x ULN AND **Alkaline phospatase** <2x ULN (potential Hy's Law indicators of drug-induced liver damage)	• Hold **neratinib**. • The patient should return to the investigational site and be evaluated by clinical laboratory tests as soon as possible, preferably within 48 hours from awareness of the abnormal results.	• No dose adjustment required unless Childs-Turcott-Pugh Class B criteria met	• No dose adjustment required
	• Contact the Sponsor immediately to discuss next steps, including evaluation of alternative causes, and management of IP. • These events must be reported as SAEs.		

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

Table 13: Left Ventricular Ejection Fraction Toxicity Related to Trastuzumab Requiring Dose Adjustment

	Absolute Decrease from Baseline		
Relationship of LVEF to LLN	**<10%**	**10%-15%**	**>16%**
Within normal limits	Continue	Continue	Hold[a]
1% - 5% below LLN	Continue	Hold[a]	Hold[a]
>6% below LLN	Continue	Hold[a]	Hold[a]

[a] Repeat LVEF assessment after 4 weeks. If criteria for continuation were met, trastuzumab is resumed. If not (ie, 2 consecutive holds) or a total of 3 holds occurred, trastuzumab is permanently discontinued.

Table 14: Symptomatic Cardiac Failure Toxicity Related to Neratinib or Trastuzumab Requiring Dose Adjustment

NCI CTCAE V4.0	Action with Neratinib	Action with Trastuzumab
Symptomatic cardiac failure	**Neratinib should be discontinued.**	**Trastuzumab should be discontinued**

Table 15: Infusion Reactions Related to Trastuzumab Requiring Dose Adjustment

NCI CTCAE V4.0	Action with Trastuzumab
Grade 1 / 2 Hypersensitivity reactions	• Decrease the rate of infusion for mild to moderate infusion reaction. • Interrupt the infusion if necessary. • Treat as per institutional policy. Patients should be evaluated and carefully monitored. When symptoms resolve to ≤ Grade 1, infusion may be resumed (maintain dose) later that day at a slower rate or on the next day at slower rate with premedication. • Premedication should be used for all subsequent treatments.
Grade 3 Severe infusion reactions	• Discontinue trastuzumab infusion permanently.

5.3. Packaging, Labeling and Storage

Detailed packaging information is available in the study manual. The IPs will be labeled according to local regulations.

5.3.1. Neratinib

Neratinib will be supplied as 40-mg film-coated tablets packaged in opaque, plastic bottles with desiccant and a child-proof lid.

Neratinib will be stored at 25°C (77°F) or below with desiccant; do not freeze. Excursions are permitted to 30°C (86°F). Neratinib should be stored in a secure location with limited access. Patients should be instructed to store neratinib in a safe place at room temperature.

5.3.2. Fulvestrant

The Sponsor may provide commercial supply of fulvestrant, labeled for clinical trial use. Clinical sites that are not allowed to accept commercially available product may utilize their own

commercial supply. The pharmaceutical form of fulvestrant is clear, colorless to yellow, viscous solution.

Pre-filled syringe of fulvestrant should be stored in the original packaged container to protect from light in refrigerator at (2°C-8°C).

The commercially available fulvestrant is supplied in two clear Type 1 glass pre-filled syringe presentation.

5.3.3. Trastuzumab

The Sponsor may provide commercial supply of trastuzumab vials labeled for clinical trial use. Clinical sites that are not allowed to accept commercially available product may utilize their own commercial supply. Trastuzumab is supplied as a lyophilized sterile powder to be reconstituted for IV infusion. Trastuzumab should be stored in a refrigerator at (2°C-8°C).

5.4. Drug Accountability

The study site must maintain accurate records documenting dates and quantities of IP received from the Sponsor. Records must be maintained on a per-patient basis documenting dates and quantities of IP dispensed and returned at the beginning and end of each visit. Any IP accidentally or deliberately destroyed must be documented. Records also must be maintained of all IPs received and dispensed such that the amount of IP present within the pharmacy is accurate at any point in time against this record.

Reconciliation will be made throughout the study between the amounts of IP supplied, dispensed, returned, and subsequently destroyed or returned to Sponsor. All IPs will be returned to Sponsor or its representative or destroyed at the site in accordance with local standard operating procedures, as specified in writing by the Sponsor.

Individual patient dosing compliance should be reviewed at each study visit by study site staff. If patient noncompliance is noted, the patient should be re-instructed regarding proper dosing procedures in order to continue in the study. If repeated noncompliance is noted, additional steps may be taken, including withdrawal of the patient from the study (see Section 9.2).

6. CONCOMITANT TREATMENT

All combination therapies, concomitant treatments, non-drug interventions, and medications will be captured from the signing of the informed consent form (ICF) until the end of the treatment (EOT). This will include the start date, stop date, generic name, route of administration, dose, frequency and indication for treatment.

At screening, patients will be asked 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 or have taken since their last visit.

6.1. Required Concomitant Treatment

Diarrhea is the major dose-limiting toxicity of neratinib with onset typically occurring during the first few weeks of treatment. In particular, after the implementation of diarrhea prophylaxis with loperamide, most episodes of Grade 3 diarrhea occur during the first cycle of therapy (Neratinib IB; Ustaris et al, 2015). Primary prophylactic use of antidiarrheal medication is mandatory for all enrolled patients taking neratinib. Loperamide is the recommended standard therapy to prevent and treat diarrhea in this study. If alternative antidiarrheal medication is proposed, this should be discussed with the Medical Monitor and the reason documented in the source documents. Second-line antidiarrheal treatments and adjunctive therapies (ie, diphenoxylate hydrochloride and atropine sulfate [Lomotil], or octreotide [SANDOSTATIN®]) (or equivalent, as approved by the Sponsor) are also recommended for use when appropriate.

6.1.1. Loperamide

All patients receiving neratinib will take loperamide for the first 2 cycles of neratinib treatment. Patients will take 4 mg three times a day (TID) on Days 1-14 of Cycle 1 with the first dose of loperamide given concomitantly with the first dose of neratinib. After two weeks on study, patients will take loperamide 4 mg twice a day (BID) until the completion of Cycle 2 (42 days for trastuzumab containing regimens and 56 days for non-trastuzumab-containing regimens). Thereafter, loperamide will be administered as needed throughout neratinib treatment. Recommended loperamide dosing is listed below in Table 16.

Patients randomized to fulvestrant or fulvestrant and trastuzumab will not be required to take loperamide.

Table 16: Loperamide Dosing for Neratinib Treatment

Loperamide Dose	Day
4 mg TID with a total daily dose of 12 mg	Days 1-14
4 mg BID with a total daily dose of 8 mg	Days 15-end of Cycle 2
Daily dose as needed (not to exceed 16 mg per day)	Day 42+ for trastuzumab-containing regimens Day 56+ for non-trastuzumab-containing regimens

Patients must use a diary to record intake of loperamide during the first 2 cycles. Loperamide pill counts will be conducted only during the first 28 days of therapy.

6.1.2. 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 16 mg per day) with the goal of titrating to 1-2 bowel movements a day.

- Diarrhea
  - For patients who develop diarrhea during Cycle 1, loperamide should be increased up to a maximum of 16 mg a day.
- Constipation
  - 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 constipation due to loperamide are listed in Table 17.

Table 17: 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

6.1.2.1. Loperamide Antidiarrheal Therapy

The Investigator must review with the patient the **Patient Instructions** for the management of diarrhea and the **Patient Diary** for the patient's daily recording of IP dose, any adverse reactions, the number of stools, and the use of loperamide and/or other antidiarrheals. A copy of the Patient Instructions are to be handed to the patient before leaving the site with IP on or before the first day on neratinib, 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.

Documentation of the number of stools at baseline should be captured in the patient's record. Any occurrences of loose stools, diarrhea or constipation must be documented by the patient as precisely as possible and captured in the Patient Diary. The entries in the Patient Diary should be reviewed by the study staff together with the patient at the end of the first month of neratinib therapy.

The **Patient Diary** will contain details of the daily number of unformed stools the patient has experienced since the last visit. Documenting the toxicity grade of the diarrhea or constipation by the study staff needs to be reported accurately on the Case Report Form (CRF) using an adjusted NCI CTCAE version 4.0 criteria (see Section 5.2). Also, the daily dose of loperamide (or other antidiarrheals, if applicable) noted on the diary will be reviewed and recorded on the CRF.

Loperamide will be provided and dispensed directly by the site on or before C1D1 with neratinib. It is very important to initiate treatment with loperamide concomitantly with the first dose of neratinib to minimize the occurrence and severity of diarrhea.

Prophylactic dosing instructions (Cycles 1 and 2)

- Inform patients that they will experience diarrhea while taking neratinib.
- Administer loperamide: 4 mg TID for the first 14 days, with the first dose administered concomitantly with the first dose of neratinib. After two weeks, take loperamide 4 mg BID until the end of the second cycle of therapy regardless of whether the patient is experiencing diarrhea or not.
- For patients with persistent Grade 1 diarrhea (<4 stools per day above baseline) on loperamide, increase loperamide up to 16mg daily (4 mg four times a day [QID]). Lomotil® (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 to 8 hours may be added (or equivalent as approved by Sponsor).
- For Grade 2 diarrhea during Cycle 1 (4 to 6 stools per day above baseline, despite intensive anti-diarrheal therapy), consider adding octreotide (short-acting) 150 µg subcutaneous [SC] injection 3 times a day, or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg by IM injection (equivalent medication may be used with approval of the Sponsor).
- The sites must contact the patient by phone 1 day, 2 days, and 3 days after the first dose of neratinib in Cycle 1 to inquire about any diarrhea and ensure the patient is compliant with anti-diarrheal therapy.

  (**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 on the Patient Diary the number of stools per day and the dose of any anti-diarrheal medication taken each day for the first cycle of therapy (see Section 5). Patients must record all doses of neratinib for the entire duration of the study.

For new onset, uncomplicated Grade 1 or Grade 2 diarrhea in Cycle 3 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 a low-fat regimen enriched with bananas, rice, applesauce and toast until the 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 or 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, increase loperamide up to 16 mg (4 mg QID) and Lomotil (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 hours 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 TID; or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg IM (equivalent medication may be used with approval of the Sponsor).

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

Dietetic measures (same as above)

Pharmacologic treatment

- Administer loperamide: initial dose of 4 mg (2 tablets or capsules) with the first bout of diarrhea followed by 2 mg (1 tablet or 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 Grade 3-4 diarrhea on loperamide, consider administration of Lomotil (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 hours to 8 hours may be added (or equivalent as approved by the Sponsor).
- Administer octreotide (100 to150 µg SC BID or IV (25 to 50 µg/h) if dehydration is severe, with dose escalation up to 500 µg SC TID.
- Use IV fluids as appropriate.
- Consider prophylactic antibiotics as needed (eg, fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3 to4 neutropenia.

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

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

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 medications (Section 6.3), or drugs with potential for drug-drug interactions (Section 6.4), or in the associated Appendices 3 (cytochrome P450 inhibitors and inducers), 4 (p-glycoprotein substrates and inhibitors) and 5 (drugs associated with QT/QTc prolongation), is permitted at the Investigator's discretion.

Specifically, the following treatments are permitted during the study:

- 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.
- **Bisphosphonates and receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors (eg, denosumab)**, regardless of indication, provided patients have been on stable doses for at least 2 weeks prior to enrollment. The stable dose should be maintained during the IP treatment period. Patients requiring initiation of bisphosphonate treatment during the course of the study should be discontinued due to progressive disease (PD), unless disease progression can be completely ruled out and clearly documented in the patient's source documentation.
- **Secondary prophylactic use of growth factors** (eg, granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor) may be implemented per the currently applicable ASCO and the European Organization for Research and Treatment of Cancer (EORTC) (Aapro et al, 2011) guidelines at the Investigator's discretion, if significant neutropenia or febrile neutropenia/infection is observed.

6.3. Prohibited Concomitant Treatment

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

Other than as specified in protocol, any concurrent chemotherapy, radiotherapy (including palliative radiotherapy), surgery related to cancer, anticancer immunotherapy, or other anticancer treatments including other investigational agents are prohibited. Megestrol®, bisphosphonates, and RANK-ligand inhibitors are permitted provided the patient has been on a stable dose for at least 2 weeks prior to the start of neratinib. Patients with breast cancer on a stable dose of hormonal therapy will be permitted to remain on this regimen through their participation in the study.

6.4. Potential for Drug-Drug Interactions

Patients should avoid agents known to be strong cytochrome P450 (CYP) 3A4 inducers or inhibitors (eg, ketoconazole) for the duration of the active phase of the study. Patients should also avoid grapefruit and herbal remedies, including St John's Wort. Refer to Appendix 3 for a list of inhibitors and inducers of CYP isoenzymes. If unavoidable, patients taking such agents should be monitored closely.

Patients taking digoxin, a P-glycoprotein (P-gp) substrate with a narrow therapeutic window, should be monitored closely. The digoxin dose should be adjusted as needed, since neratinib is an inhibitor of P-gp. Co-administration of neratinib with digoxin could result in increased digoxin levels and associated digoxin toxicity. Refer to Appendix 4 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 5 for a summary of drugs known to have a risk of causing QT/QTc prolongation, potentially causing TdP.

Patients taking oral coumarin-derivative anticoagulants (eg, warfarin and phenprocoumon) 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 neratinib doses 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. STUDY ASSESSMENTS

7.1. Efficacy Assessments

For cohorts receiving combination treatment that includes trastuzumab (Table 2 and Table 3), post-treatment disease assessment by CT or magnetic resonance imaging (MRI) will be conducted at the beginning of Week 10 (ORR_{first}), and every 3 cycles (± 7 days) thereafter (Appendix 1 Table A1.1 and Table A1.2). For all other cohorts not receiving trastuzumab (Table 4 and Table 5), post-treatment disease assessment will be conducted at the beginning of Week 9 (ORR_{first}), and every 2 cycles (± 7 days) thereafter (Appendix 1 Table A1.1 and Table A1.2). Complete or partial response (CR or PR) must be confirmed with a repeat scan performed no sooner than 4 weeks after the criteria for response are first met. In cases where the subject discontinues treatment for reasons other than progressive disease (eg., adverse event, patient choice, noncompliance, etc.) and the response is either CR or PR, then a confirmation scan is required no sooner than 4 weeks after the criteria of response is met. Radiological response is assessed by RECIST v1.1. Following one year on therapy, scans may move to every 4 cycles for trastuzumab-containing regimens and every 3 cycles for non-trastuzumab containing regimens. Following two years on therapy, scans may move to every 5 cycles for trastuzumab-containing regimens and every 4 cycles for non-trastuzumab containing regimens.

For patients who enrolled prior to Amendment 6, the same method of measurement (eg PET/CT) and same method of disease assessment (eg metabolic response by PET Response Criteria) should continue through final assessments

7.1.1. Tumor Assessments

Radiographic tumor assessments use CT (or MRI or PET/CT) and tumor markers will be performed in accordance with the Schedule of Procedures (Appendix 1 Table A1.1 and Table A1.2). Following one year on therapy, scans may move to every 4 cycles for trastuzumab-containing regimens and every 3 cycles for non-trastuzumab containing regimens. Following two years on therapy scans may move to every 5 cycles for trastuzumab-containing regimens and every 4 cycles for non-trastuzumab containing regimens.

7.1.1.1. General Information

All target and nontarget sites of disease (see Appendix 6) identified at screening must be followed for the duration of the study. Their size, presence, and absence should be noted throughout follow-up. Overall response for each patient is based on the combined results for target and nontarget lesions and the presence or absence of new lesions.

Tumor-based efficacy endpoints (ie, PFS, ORR_{first}, and confirmed ORR) will be based on tumor assessments performed by the Investigator. Response and progression will be evaluated using RECIST version 1.1 (see Appendix 6).

Tumor assessments will be performed for all patients as described in Section 7.1 and in (Appendix 1 Table A1.1 and Table A1.2) throughout the treatment phase until the occurrence of documented disease progression, death or patient withdrawal from the study (ie, lost to follow-up, withdrawal of consent), whichever occurs first (refer to Section 9 for a complete list of reasons for withdrawal from the study). Additional tumor evaluations may be performed as clinically indicated. Missed tumor assessments must be performed as soon as possible. As soon

as evaluations for each tumor assessment are completed, the Investigator should assess the patient's overall response (target and nontarget lesions) based on appropriate disease response criteria and overall response algorithms (see Appendix 6). Scans must be assessable for all evaluations.

The longest diameters (LD) for all target lesions will be recorded (short axis for target pathological lymph nodes) within the source documentation. The LD for all target lesions will be added and reported as the baseline sum LD (SLD). Per RECIST version 1.1, for determining CR or PR, all post-baseline tumor measurements will be compared with the baseline SLD; for determining PD, the post-baseline measurement is compared with the smallest SLD recorded since initiation of treatment, including baseline (Appendix 6).

Patients who discontinue study treatment and do not have PD will be asked to remain on study for tumor evaluation per protocol and for determination of progression free survival (PFS; see Section 8.3).

7.1.1.2. Radiographic/Imaging Evaluations

The same method of measurement (eg, CT or MRI) and the same technique of assessment should be used to characterize each identified and reported lesion at baseline through the final visit. All measurements should be taken, recorded, and measured on computer screens of Picture Archival Communication (PAC) systems or on hard-copy images using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of the active drug phase and never more than 28 days before the beginning of the active drug phase. As often as possible, lesions should be assessed by the same Investigator or same radiologist using the same method of measurement. Physical examination may not be the sole method of assessment for a solitary lesion. For patients with measurable and evaluable skin lesions, photographs should be taken, inclusive of a ruler.

All patients must have a CT of the chest, abdomen and pelvis at baseline. Additional areas of assessment at baseline would include additional possible target or non-target lesion. On-study scans should be repeated at the appropriate interval for areas with known target or non-target disease. Additional fields of imaging should be repeated as clinically indicated. Patients with a history of brain metastasis must receive a Brain MRI or CT at baseline. Follow-up Brain MRI or CT scans should only be completed as clinically indicated.

Definitions of measurable disease and measurable lesions, documentation of "target" and "nontarget" lesions, and evaluation of response are summarized in Appendix 6 (Eisenhauer, et al, 2009).

Baseline screening radiographic studies and all subsequent radiographic studies and their associated reports will be collected and stored by the Sponsor for possible future independent review.

7.1.2. Tumor Assessments – Clinical

Clinical examination should include caliper measurement when lesions are superficial. Lesions that cannot be measured with calipers should be recorded as non-measurable. Documentation by color photography in good light and including a ruler to estimate the size of the lesion is required.

Note that when lesions can be evaluated by clinical examination and imaging, imaging evaluation should be undertaken by CT or MRI as appropriate.

7.1.3. Quality of Life Assessments

Patient reported outcomes using the FACT-G (Appendix 8) assessment will be performed at screening, C1D1, and at the beginning of each cycle (per office visit, prior to drug administration) for up to 6 months or end of treatment, whichever comes first.

7.1.4. ECOG Performance Status

The ECOG performance status will be assessed in accordance with the Schedule of Procedures (Appendix 1 Table A1.1 and Table A1.2). The ECOG categories are summarized in Appendix 2.

7.2. Safety Assessments

Refer to the Schedule of Procedures (Appendix 1 Table A1.1 and Table A1.2) for time points. The following safety endpoints will be assessed: Medical history, AEs, vital signs, detailed/brief (system-guided) physical examinations, 12-lead ECGs, LVEF (via ECHO or MUGA), and laboratory evaluations.

AEs will be graded according to the NCI CTCAE version 4.0. SAEs will be reported until 28 days after the last dose of IP(s) and will be followed until resolution. 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. More details on AEs can be found in Section 12.

The diary used for recording of IP intake will also be used by patients to document any other study treatment. In case of diarrhea, the diary also serves to document the number of loose stools per day and use of loperamide/other antidiarrheal treatments taken.

7.2.1. Laboratory Assessments

Laboratory testing will be performed in accordance with the Schedule of Procedures (Appendix 1 Table A1.1 and Table A1.2).

The institutional laboratory will analyze all hematology, routine blood chemistry, and urine samples collected. Samples will be analyzed at a facility meeting Good Laboratory Practice (GLP) requirements as evidenced by current accreditation by an independent testing organization.

Laboratory assessments are not required on C1D1 if previously obtained within 72 hours prior to C1D1 as part of screening, with no clinically significant findings.

The following laboratory parameters will be determined, as summarized in Table 18.

Table 18: Laboratory Parameters

Hematology:	Hematocrit (Hct) Hemoglobin (Hb) Platelet count Red blood cell (RBC) count White blood cell (WBC) count, with differential	
Clinical chemistry:	Albumin Alkaline phosphatase Alanine transaminase (ALT) Aspartate transaminase (AST) Blood urea nitrogen (BUN) Calcium Chloride Serum Creatinine Glucose (non-fasting)	Lactate dehydrogenase (LDH) Magnesium Phosphorus Potassium Serum total cholesterol (non-fasting) Sodium Total bilirubin Total protein
Urinalysis (dipstick or laboratory analysis; microscopic examination if abnormal):	Blood Protein Glucose	
Serum or urine pregnancy test:	In women of child-bearing capacity (at screening and repeated only if performed outside 72 hours of C1D1).	

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the Investigator and/or the Sponsor Medical Monitor (or his/her designated representative), or until a diagnosis that explains them is made.

Criteria for reporting abnormal laboratory values as AEs are summarized in Section 12.1.2. For all laboratory values that are outside of the laboratory's reference range, the Investigator (or designee) must record CS (clinically significant) or NCS (not clinically significant) on the laboratory sheet.

7.2.2. Vital Signs

The following vital signs will be assessed in accordance with the Schedule of Procedures (Appendix 1 Table A1.1 and Table A1.2):

- Blood pressure (systolic and diastolic; mmHg)
- Resting heart rate (beats per minute)
- Respiration rate (breaths per minute).
- Body temperature (°C)
- Weight (kg)
- Height, cm (Screening only)

7.2.3. Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Procedures (Appendix 1 Table A1.1 and Table A1.2).

The detailed/brief (system-guided) physical examination will evaluate any clinically significant abnormalities; including worsening of medical history conditions.

7.2.4. Electrocardiograms

Single standard 12-lead digital ECGs will be performed in accordance with the Schedule of Procedures (Appendix 1 Table A1.1 and Table A1.2).

- For the baseline assessment, ECG will be performed within 14 days prior to C1D1 for all cohorts. Patients will have ECGs performed only at baseline and at end of treatment.

The ECG will include heart rate, rhythm and RR, PR, QRS, and QTc intervals. The ECG will be read and interpreted at the investigational site for patient safety monitoring, and documentation stored with the source documents. Each ECG will be reviewed by the Investigator or delegate who will document this review by his/her initials and date. The Investigator (or delegate) will record CS (clinically significant) or NCS (not clinically significant) on each non-normal ECG.

7.2.5. Left Ventricular Ejection Fraction (LVEF)

The MUGA scan or ECHO scan to determine LVEF will be performed in accordance with the Schedule of Procedures (Appendix 1 Table A1.1 and Table A1.2).

- The Screening MUGA/ECHO scans to determine LVEF will be performed as routine procedures within 28 days before C1D1.
- For any cohort treated with trastuzumab (Table 2 and Table 3): following Screening, MUGA/ECHO scans will be performed every 12 weeks (+/- 7 days) and at end of treatment.
- For all other cohorts not receiving trastuzumab (Table 4 and Table 5): MUGA/ECHO scans will be performed at screening and at end of treatment.

It is strongly recommended to use the same method of cardiac evaluation (ECHO or MUGA) at each time point for each patient.

7.2.6. Archival and Fresh Tumor Tissue, Whole Blood (for Germline DNA), and Plasma Collection

Biospecimen collections will be performed in accordance with the Schedule of Procedures (Appendix 1 Table A1.1 and Table A1.2). All specimens should be processed, packaged and shipped according to the Laboratory Manual.

Archival and/or Fresh Tumor Tissue:

All efforts will be made to collect archival and/or fresh pretreatment (screening) tumor tissues (except for breast cancer and NSCLC cohorts where collection of a pretreatment

biopsy is mandatory), and, if possible, upon disease progression for analysis as outlined in the Exploratory Objectives of the protocol.

Whole Blood for Germline DNA:

Blood will be obtained during the study (preferably acquired during screening, at the same time as hematology, serum chemistry, and plasma samples are taken).

Plasma for Biomarker Analysis of cfDNA:

Serial plasma samples for subsequent exploratory biomarker analyses will be collected from each patient during the 3 phases of the study:

1. Pretreatment (preferably acquired during screening, or at the latest on C1D1 but **before the patient takes their first neratinib monotherapy or combination therapy**),
2. On-treatment and
3. Post-treatment (coordinated with EOT).

It is expected that these banked plasma specimens will subsequently be used for cfDNA mutational analysis to investigate mechanisms of primary and/or acquired resistance to neratinib therapy.

7.3. Protocol Deviations

Protocol deviations should be reported to the Sponsor (or designee) as they occur or are discovered.

7.4. Patient Diary

A Patient Diary will be provided by the Investigator for the patient to record daily intake of neratinib for every cycle, loperamide (and/or other antidiarrheal medication) only for the first two cycles of treatment and the frequency of diarrhea.

8. STUDY CONDUCT

Schedule of Procedures is provided in (Appendix 1 Table A1.1 and Table A1.2).

In addition to the procedures listed in this section, unscheduled clinic visits and procedures should be performed at the Investigator's discretion to assess symptoms and concerns newly reported by the patient to rule out or confirm potential recurrence, or for the purpose of assessing the patient's safety.

8.1. Informed Consent

Before any study procedures are performed, obtain informed consent, as required by the IRBs/ECs and regulatory authorities.

8.2. Screening All Cohorts

Screening activities are to be conducted within 14 days prior to C1D1, except for CT, PET/CT or MRI disease assessment (within 28 days prior to C1D1), ECHO/MUGA (within 28 days prior to C1D1), a serum or urine pregnancy test (at screening, and to be repeated if performed outside 72 hours of C1D1). In breast cancer and NSCLC patients, fresh tumor biopsy should be obtained within 28 days prior to C1D1 and for all other cohorts, archival and/or fresh pretreatment tumor tissue should be obtained during screening or within the first cycle of treatment.

The following information/assessments will be collected/recorded at Screening:

- Medical history:
  - Presence of chronic conditions and/or medical history of significance (include review of history of cardiac, pulmonary, and gastrointestinal disease) including smoking history (only for NSCLC patients), relevant surgical procedures, or symptoms experienced during the previous 30 days and those ongoing at the time of screening, and any medical conditions that require medication. Identify start of current medical conditions by at least a year.
  - Cancer history, including but not limited to, date of first diagnosis, nodal status (based on pathologic assessment of nodes at the time of surgery, either before adjuvant chemotherapy or after completion of neoadjuvant chemotherapy), histology, tumor stage at diagnosis, previous chemotherapy/ biotherapy/immunotherapy, previous adjuvant therapy, drug names, start and stop dates, reason for treatment discontinuation, previous radiation, and prior cancer related surgical therapies.
  - Other previous and concomitant medication will be documented, as described in Section 6.
- Demography: date of birth, sex, race (Asian, Black or African American, White, Other).
- Physical examination. Refer to Section 7.2.3.
- Vital signs, including height and weight. Refer to Section 7.2.2.
- ECG. Refer to Section 7.2.4.

- ECHO or MUGA (to obtain LVEF). Refer to Section 7.2.5.
- Laboratory tests (hematology and serum chemistry, urine test by dipstick or laboratory analysis, urine or serum pregnancy in women of child-bearing capacity [at screening and repeated on C1D1 prior to treatment if performed >72 hours prior to C1D1]). Refer to Section 7.2.1.
- Archival and/or fresh tumor tissue sample and whole blood collection from all patients for centralized *ERBB* mutation and amplification. Refer to Section 7.2.6.
- Baseline pretreatment plasma sample for exploratory biomarker analysis. Refer to Section 7.2.6.
- Whole blood DNA sample for exploratory biomarker analysis. Refer to Section 7.2.6.
- Quality of Life Assessments. Refer to Section 7.1.3.
- ECOG performance status. Refer to Section 7.1.4.
- Radiographic tumor assessment within 28 days prior to C1D1. Refer to Section 7.1.1.

The C1D1 physical examination, ECOG performance status, and laboratory tests may be omitted if the screening values were obtained within 72 hours prior to initiation of treatment.

8.2.1. Active Treatment Stage

For patients enrolled to a neratinib containing cohort, neratinib will be self-administered by patients daily. For study cohorts where neratinib will be administered in combination with another therapy, combination treatment will consist of neratinib plus trastuzumab, and neratinib plus fulvestrant plus trastuzumab at dose regimens and cycle lengths described in Section 5, and in accordance with the Schedule of Procedures provided in (Appendix 1 Table A1.1 and Table A1.2).

In the study cohorts where single agent fulvestrant or fulvestrant plus trastuzumab will be administered at dose regimens and cycle lengths described in Section 5, and in accordance with the Schedule of Procedures provided in (Appendix 1 Table A1.1 and Table A1.2).

The following will be performed in accordance with the Schedule of Procedures provided in (Appendix 1 Table A1.1 and Table A1.2):

- Physical examination. Refer to Section 7.2.3.
- Vital signs and weight. Refer to Section 7.2.2.
- Laboratory tests. Refer to Section 7.2.1.
- ECOG performance status. Refer to Section 7.1.4.
- Radiographic tumor assessment. Refer to Section 7.1.1.
- Plasma sample for exploratory biomarker analyses. Refer to Section 7.2.6.
- Treatment compliance assessment. Refer to Section 7.4.
- Review compliance with loperamide antidiarrheal therapy. Refer to Section 6.1.
- AE assessment. Refer to Section 12.

- Concomitant medication assessment. Refer to Section 6.
- Dispense and collect IP. Refer to Section 5.4.
- ECG. Refer to Section 7.2.4.
- ECHO or MUGA (to obtain LVEF). Refer to Section 7.2.5.
- Health Outcomes Assessment. Refer to Section 7.1.3.

8.2.2. End of Treatment Visit for All Cohorts

After the end of treatment (EOT), the following assessments should be scheduled 28 days (+14 days) after the last dose of IP(s), in accordance with the Schedule of Procedures in (see Table A1.1 and Table A1.2). If the patient is unable or unwilling to undergo any assessment, the last assessment on record will be used as end of treatment assessment.

- Physical examination. Refer to Section 7.2.3.
- Vital signs, including weight. Refer to Section 7.2.2.
- ECG. Refer to Section 7.2.4. ECHO or MUGA (obtain LVEF). Refer to Section 7.2.5.
- Laboratory tests (hematology, chemistry). Refer to Section 7.2.1.
- Plasma sample for exploratory biomarker analyses. Refer to Section 7.2.6.
- Radiographic tumor and response assessment should be collected for patients discontinuing treatment for any reason other than radiological disease progression. Refer to Section 7.1.1.
- AE assessment. Refer to Section 12.
- Concomitant medication assessment. Refer to Section 6.
- Treatment compliance assessment. Refer to Section 5.4.
- Optional tumor biopsy. Refer to Section 7.2.6 .

Patients will enter the Follow-up Stage after these EOT assessments.

8.3. Long-term Follow-up for All Cohorts

After the end of treatment, patients who do not withdraw consent will enter the long-term Follow-up Stage.

These patients will be followed for PFS and survival status during the long-term follow-up phase. The following will be performed in accordance with the Schedule of Procedures (Appendix 1 Table A1.1 and Table A1.2):

- Continue to monitor AEs until the 28th day after the last dose of IP(s).
- Anti-cancer medications taken since last contact.

- For patients who discontinued treatment for any reason other than disease progression, collect radiographic tumor and response assessments until documented disease progression, death or withdraw of consent. Refer to Section 7.1.1.
- After disease progression, follow patients via clinic visits, email or phone calls every 12 weeks (±14 days) after each patient's last dose of treatment. Patients who received trastuzumab will continue cardiac monitoring with ECHO or MUGA scanning every 6 months up to 24 months after the last dose of trastuzumab.
- If a patient withdraws from the follow-up portion of the study, the primary reason for discontinuation should be documented (see Section 9.3).

8.4. End of Study

The EOS will occur when all patients have been followed for OS or death, withdrawal of consent, or are lost to follow-up. The Sponsor reserves the right to terminate the study early for any reason and offer patients receiving treatment benefit the option to continue to receive neratinib via a separate treatment extension study or an expanded access protocol.

9. PATIENT WITHDRAWAL AND REPLACEMENT

9.1. Investigational Product Discontinuation

Patients **must** be discontinued from the **investigational products** (but may remain in the study for long term follow up, if appropriate), under the following circumstances listed in this section and in Section 5.2, unless otherwise agreed with the Medical Monitor:

- If the patient requires more than 2 dose reductions of IP (see Section 5.2).
- If the IP is withheld due to a neratinib-related AE for >28 days. Patients who are clinically benefiting from therapy with neratinib may be resumed on therapy after 28 days if approved in advance by the Sponsor.
- Disease progression. Patients who, in the opinion of the Investigator, are continuing to benefit from neratinib despite disease progression may continue to receive neratinib if approved in advance by the Sponsor. Patients who are initially enrolled to a non-neratinib containing arm may remain on study and receive neratinib, fulvestrant and trastuzumab at the time that the local investigator determines the patient has unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease related symptoms before the first scan post-treatment.
- Pregnancy (see Section 12.4).
- Investigator request.
- Patient request (ie, withdrawal of consent for treatment).

Withdrawal due to AE should be distinguished from withdrawal due to other causes and recorded on the appropriate AE case report form (CRF) page.

In the case of the following events, the patient should discontinue treatment, but should be asked to remain on study for response assessment as well as PFS if the event leading to discontinuation of treatment occurs prior to the first post-baseline tumor assessment, or for response assessment, PFS, and OS if the event occurs after the first tumor evaluation:

- Adverse events/toxicity
- Symptomatic deterioration
- Major protocol violation
- Patient request
- Investigator request (reasoning required)

9.2. Withdrawal from the Study

Patients may withdraw from the entire study including follow-up at any time without penalty and for any reason without prejudice to his or her future medical care.

Patients may be required to withdraw from the study after discussion with the Sponsor and/or Investigator (whenever possible) for the following reasons:

- At the discretion of the Investigator.

- At the patient's request (withdrawal of consent for the study). See Section 9.3 for withdrawal procedures.
- Individual patient dosing noncompliance.
- Lost to follow-up (defined as receiving no response after three attempts at contact by phone followed by one attempt by sending a certified letter).
- If the entire study is terminated prematurely as described in Section 10.

A patient may also be withdrawn from **investigational product/study** by the Sponsor, Regulatory Authorities, or Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs).

9.3. Procedures for Investigational Product Discontinuation/Study Withdrawal

When a patient is withdrawn from the study, the Investigator will notify the Sponsor promptly. In all cases, the reason(s) for premature discontinuation/withdrawal, and the primary reason must be recorded on the CRF. If a patient is prematurely withdrawn from the IP or the study for any reason, the Investigator must make every effort to perform the evaluations described for the EOT visit (performed 28 days [+14 days] after the last dose of study drug, as appropriate), and Follow-Up Visits as described in (Appendix 1 Table A1.1 and Table A1.2). If a patient discontinues due to an AE, he/she should be strongly encouraged to undergo the EOT assessment and continue to be under medical supervision until symptoms/signs cease or the condition becomes stable.

If a patient withdraws consent but agrees to undergo a final examination, this will be documented on the Investigator's copy of the ICF, which will be countersigned and dated by the patient. If a patient withdraws consent due to an AE, the reason for discontinuation should be identified as 'Due to AE.'

If a patient is lost to follow-up, or voluntarily withdraws from study participation, every effort should be made to determine why a patient is lost to follow-up or withdraw consent.

All patients will remain on active study treatment until a cause of early treatment discontinuation occurs; these include disease progression, unacceptable toxicity, and withdrawal of consent (Section 9.1), or at Investigator discretion. Upon confirmed disease progression, or discontinuation of IP for any other reason, all further treatment for the patient's cancer will be at the Investigator's discretion, and all patients will remain in follow-up for PFS and survival, unless consent has been withdrawn.

10. PREMATURE TERMINATION OF THE STUDY

The Sponsor may suspend or terminate the study or any part of the study at any time for any reason. The IP will be available to patients who continue to receive clinical benefit following the EOS as described in Section 8.4.

If the Investigator suspends or terminates the study, the Investigator will promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. The Investigator will also return all of the IP, IP containers, and other study materials to the Sponsor or have them destroyed according to Sponsor guidelines. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC and regulatory agency with final reports and summaries as required by regulations. For investigational new drug application studies, the Investigator must submit a written report to the Sponsor and the IRB/IEC within 3 months after the completion or termination of the study.

11. STATISTICAL METHODS

The statistical considerations summarized in this section outline the plan for data analysis of this study. The Statistical Analysis Plan (SAP) will provide additional detail.

11.1. Sample Size Justification

11.1.1. Sample Size Justification for the Randomized HR+ and with Prior CDK4/6i Breast Cancer Study Cohort:

A Simon's 2-stage optimal design (Simon, 1989) will be used to determine whether there is sufficient activity to warrant further development of the therapy and to minimize the number of patients exposed to therapy if ineffective. For each treatment arm, using Simon's 2-stage optimal design (with significance level 10% and power of 80%), an ORR (confirmed) of 10% or less per RECIST by independent assessment will be considered unacceptable (null hypothesis) whereas an ORR (confirmed) of 30% per RECIST v1.1 by independent assessment will merit further study (alternative hypothesis). In the first stage, 7 patients are enrolled in each treatment arm. If at least 1 response is observed in the first stage, the second stage in the treatment arm will be opened. In the second stage, 11 additional response evaluable patients will be accrued and randomized for a total of 18 patients in the treatment arm. The null hypothesis will be rejected (for each arm separately) if at least 4 responses are observed in Stage 2 for each arm.

Once the Simon's 2-stage criteria are met, enrollment of the neratinib arm may continue until up to 50 patients have been enrolled. A sample size of 50 patients provide a 95% CI of (17.9%, 44.6%) when the ORR is 30%.

11.1.2. Sample Size Justification for All Other Cohorts:

A Simon's 2-stage optimal design (Simon, 1989) will be used to determine whether neratinib monotherapy has sufficient activity to warrant further development in the following cohorts: cervical, salivary gland, and *EGFR* exon 18 mutant non-small cell lung cancers. A similar Simon's 2-stage design will be used to determine whether neratinib combination therapy has sufficient activity to warrant further development in the following cohorts: HR+ and CDK4/6i naïve and TNBC. Early study termination will be permitted if data at the first stage indicate that the treatment is ineffective. For each cohort, using Simon's optimal 2-stage design (with significance level 10% and power of 80%), an ORR_{first} of 10% or less will be considered unacceptable (null hypothesis) whereas an ORR_{first} of 30% will merit further study (alternative hypothesis). In the first stage, enrollment will continue until 7 patients received at least one dose of study treatment and completed the first tumor assessment by the investigator (response evaluable). If no responses are observed, the second stage for the cohort must be discontinued. Otherwise 11 additional response evaluable patients will be accrued for a total of 18 patients in the cohort. The null hypothesis will be rejected (for each cohort separately) if at least 4 responses are observed in Stage 2 for each cohort.

Once the Simon's 2-stage criteria are met, enrollment to the salivary gland and *EGFR* exon 18 mutant NSCLC cohorts may continue until up to 30 patients and the enrollment into the cervical, HR+ and CDK4/6i naïve, and TNBC cohorts may continue until up to 50 patients. A sample size of 50 patients provide a 95% CI of (17.9%, 44.6%) when the ORR_{first} is 30%. A new

cohort may also be opened separately at any time per Sponsor discretion and follow the Simon's 2-stage criteria. Cohorts may close prior to planned enrollment.

11.2. Statistical Analyses

In general, efficacy and safety analyses in this study are meant to be cohort-specific and will be summarized by monotherapy and combination therapy separately. Safety analyses will also be summarized across all cohorts where appropriate.

11.2.1. Populations for Analysis

For the purpose of patient disposition, the intent-to-treat (ITT) population is defined as all patients who are enrolled into the study.

The primary analysis population is defined as all patients who received at least 1 dose of study treatment. This population will be used for all efficacy and safety analyses, if not otherwise specified.

11.2.2. Primary Endpoint

The primary endpoint for the randomized hormone receptor positive (HR+), *HER2* negative metastatic breast cancer and metastatic cervical cancer cohorts is the confirmed objective response rate (ORR) by independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. For all other cohorts, the primary endpoint is the first objective response rate (ORR_{first}) by investigator at the first post-baseline tumor assessment. The confirmed ORR and the ORR_{first} will be estimated and the associated 2-sided 95% Clopper-Pearson confidence intervals will be determined. The ORR is defined as the proportion of patients who achieve CR or PR, per RECIST version 1.1 and confirmed by repeat tumor assessment using the same criteria performed no less than 4 weeks after the initial response. The ORR_{first} is defined as the proportion of patients who achieve CR or PR, per RECIST version 1.1 or other defined response criteria, as their best overall response at the first tumor assessment.

11.2.3. Secondary Endpoints

For the randomized HR+, *HER2* negative metastatic breast cancer and metastatic cervical cancer cohorts:

- Confirmed ORR, per RECIST version 1.1, by investigator
- Duration of response (DOR), per RECIST version 1.1, by both independent central review and investigator
- Clinical benefit rate (CBR), per RECIST version 1.1, by both independent central review and investigator
- Progression-free survival (PFS), per RECIST version 1.1, by both independent central review and investigator
- For the metastatic cervical cancer cohort only, overall survival (OS)

For all other cohorts:

- Confirmed ORR, per RECIST version 1.1 or other defined response criteria, by investigator

- DOR, per RECIST version 1.1 or other defined response criteria, by investigator
- CBR, per RECIST version 1.1 or other defined response criteria, by investigator
- PFS, per RECIST version 1.1 or other defined response criteria, by investigator
- OS

For all cohorts:

- Safety and tolerability of study treatments
- Patient Reported Outcomes (PRO)

For either independent central review or investigator's assessment, the ORR is defined as the proportion of patients who achieve CR or PR as their best overall response. Complete or partial responses must be confirmed by repeat tumor assessment using same criteria performed no less than 4 weeks after the response are initially met. The confirmed ORR will be estimated and its associated 2-sided 95% Clopper-Pearson confidence intervals will be determined.

The DOR is defined as the time response criteria were met until progression or death. Median DOR will be estimated via Kaplan-Meier with its associated 2-sided 95% confidence intervals.

The clinical benefit rate (CBR) is defined as CR+PR +SD ≥16 weeks (≥24 weeks for the breast cancer patients). The CBR will be estimated, and its associated 2-sided 95% Clopper-Pearson confidence intervals will be determined.

The PFS is defined as the interval from C1D1 until the first date on which recurrence, progression, or death due to any cause, is documented, censored at the last assessable evaluation or the last evaluation before the initiation of new anticancer therapy, if applicable. Median PFS will be estimated via Kaplan-Meier with its associated 2-sided 95% confidence intervals.

Patient reported outcomes will be evaluated using the FACT-G questionnaire. The assessments will be summarized and plotted over time. Changes from baseline will be provided with both point estimates and confidence intervals.

11.2.4. Exploratory Endpoints

Archival tumor tissue will be collected from all patients for centralized ERBB mutation profiling using next generation sequencing and/or other molecular techniques. Pre-, on-, and post-treatment plasma-derived cfDNA will also be collected for exploratory biomarker analysis.

Optional biopsies (all cohorts except for all breast cancer patients and NSCLC patients where a fresh pretreatment tumor biopsy is mandatory) will be collected following disease progression and treatment discontinuation. The tissue may be subject to next-generation sequencing, gene expression profiling, immunohistochemistry and other assays to identify potential resistance mechanisms to neratinib treatment.

No formal statistical analysis is planned for these exploratory objectives.

11.2.5. Adverse Events, Serious Adverse Events, and Deaths

All AEs and SAEs will be reported until 28 days after the last dose of IP(s) and will be followed until resolution or until the condition stabilizes. AEs and SAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16 or later and tabulated by system organ class (SOC) and preferred term. All AEs will be graded by the Investigator according to

the NCI CTCAE version 4.0. All tabulations will be sorted by descending frequency of SOC and preferred term in the total column unless otherwise noted.

Cause of death and the time of death (dichotomized as within 28 days of last dose versus more than 28 days after last dose) will be summarized via frequencies and percentages. Patient death listings will include all death data available including the date of death, cause of death, and any AEs resulting in death.

11.2.6. Laboratory Results

Laboratory test results will be collected pretreatment (baseline) and until 28 days (+14 days) after the last dose of study treatment. Standard reference ranges will be used for missing or discrepant normal ranges.

Laboratory data will be summarized in tables using descriptive statistics for baseline and each cycle/visit. Descriptive statistics will be calculated on both the actual score and the change from baseline score. Additionally, clinically significant abnormalities in laboratory results will be summarized for the post-baseline cycles/visits using frequencies and percentages. Shifts in normal/abnormal status between baseline and subsequent visits will be summarized as well.

12. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

All observed or volunteered AEs regardless of treatment group or causal relationship to the IPs will be recorded on the AE page(s) of the CRF.

12.1. Definitions

12.1.1. Adverse Events

An AE is any untoward medical occurrence that occurs in a patient or clinical investigation patient administered a pharmaceutical product, and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered related to the medicinal product (definition per International Conference on Harmonisation [ICH] E2A and E6 R1).

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology on the AE CRF page. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

For all AEs, the Investigator must pursue and obtain information adequate to both determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (see Section 12.1.3) requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE.

Interventions for pretreatment conditions (eg, elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered an AE.

TEAEs are those events that occur or worsen on or after first dose of IP and up to 28 days after the last dose of IP.

12.1.2. Abnormal Laboratory Results

The criteria for determining whether an abnormal laboratory test result should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or,
- Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting as an AE), and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
- Test result leads to any of the outcomes included in the definition of a SAE, and/or
- Test result is considered to be an AE by the Investigator or by the Sponsor

Any abnormal test result that is determined to be an error does not require reporting as an AE, even if it did meet one of the above criteria except for when the test result leads to any of the outcomes included in the definition of a SAE. Clinically significant laboratory results must be recorded in the patient's CRF.

12.1.3. Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose (ICH E2A and E6 R1):

- Results in death.
- Is life-threatening.
  This means that the patient is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression will be reported if they fulfill the SAE definition.

12.1.4. Hospitalization

Any inpatient hospital admission that includes a minimum of an overnight stay to a healthcare facility meets the criteria for 'hospitalization.' Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

The following are <u>not</u> considered to be hospitalization:

- Rehabilitation facilities
- Hospice facilities
- Respite care (eg, caregiver relief)
- Skilled nursing facilities
- Nursing homes
- Routine emergency room admissions
- Same day surgeries (as outpatient /same day/ambulatory procedures)

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pretreatment lab abnormality).
- Social admission (eg, patient has no place to sleep).
- Administrative admission (eg, for yearly physical examination).
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol).
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery).
- Hospitalization for observation without a medical AE.
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual patient.
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

12.1.5. Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reactions (SUSARs) are events which are serious as per the above criteria (see Section 12.1.3 Serious Adverse Events), the nature or severity of which is not consistent with the applicable product information (Neratinib IB) and are judged by the Investigator or by the Sponsor to be related to the IP.

12.1.6. Severity Assessment

AEs will be graded by the Investigator according to the NCI CTCAE version 4.0 (Publication Date: 14-Jun-2010, https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf), according to the following general categories:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Note the distinction between the severity and the seriousness of an AE: A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it meets one of the criteria for SAEs, listed above.

12.1.7. Causality Assessment

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship in the CRF and report such an assessment in accordance with the serious adverse reporting requirements, if applicable. A suspected adverse reaction means any AE for which there is a reasonable possibility that the IP caused the AE. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the IP caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the Investigator does not know whether or not the IP caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section 12.2 and Section 12.3). If the Investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (eg, IP or other illness). The relationship of the AE to the study treatment (IP or other concomitant medications) will be assessed following the definitions below:

- 'No' (unrelated): Any event that does not follow a reasonable temporal sequence from administration of the IP AND is likely to have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- 'Yes' (related): Any reaction that follows a reasonable temporal sequence from administration of the IP AND follows a known response pattern to the suspected IP AND recurs with re-challenge, AND/OR is improved by stopping the IP or reducing the dose.

In addition, if the Investigator determines an AE is associated with study procedures, the Investigator must record this causal relationship on the AE CRF page and report such an assessment in accordance with the SAE reporting requirements, if applicable.

12.1.8. Special Reporting Situations

Safety events of interest due to the Sponsor's IP that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the IP.
- Suspected abuse/misuse of the IP.
- Inadvertent or accidental exposure to the IP.

- Medication error that may result from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength.
- Suspected transmission via the IP of an infectious agent.

Special reporting situations should be recorded on the AE CRF page. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE form and related as required (see Section 12.3).

12.2. Reporting Adverse Events

For serious and non-serious AEs, the reporting period to the Sponsor (or its designated representative) begins from the time that the patient signs the informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving IP, through 28 calendar days after the last administration of the IP.

For all AEs with causal relationship to the IP, follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at the level acceptable to the Investigator, and the Sponsor concurs with that assessment.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of the IP, irrespective of any intervening treatment.

The Sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

12.3. Reporting Serious Adverse Events

All SAEs, irrespective of relationship to the IP, must be reported within 24 hours of discovery or notification of the event to the Sponsor or designated representative using the SAE form. The SAE form must be signed by the Investigator. In particular, if the SAE is fatal or life-threatening, notification to the Sponsor must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to follow-up information on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breast feeding cases. For SAE reporting information, please refer to the Study Contact List which is provided as a separate document.

Relevant medical records should be provided to the Sponsor or its designated representative as soon as they become available; autopsy reports should be provided for deaths if available.

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.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.

- The event can be attributed to agents other than the IP or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

12.4. Pregnancy

All initial reports of pregnancy must be reported to the Sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate Exposure-In-Utero (EIU) form.

For IPs in neratinib studies, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been directly exposed (eg, environmental exposure) to the IP, or the female becomes or is found to be pregnant after discontinuing and/or being directly exposed to the IP (maternal exposure) within 28 days after last dose of or exposure to study drug. See Section 9.1 for action to be taken with IP.
- A male partner of a pregnant female has been exposed to the IP, either due to treatment or environmental exposure, within 3 months prior to the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the IP or exposure as defined above, the Investigator must submit this information on an EIU form to the Sponsor (or its designated representative) promptly. In addition, the Investigator must submit information regarding environmental exposure to an IP in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see following information related to an induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all exposure during pregnancy reports with an unknown outcome. The Investigator will follow the pregnancy until completion or until pregnancy termination (eg, induced abortion) and then notify the Sponsor or its designated representative of the outcome as a follow-up to the initial EIU form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [including that in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the neonatal death as related to exposure to IP.

Additional information regarding the exposure during pregnancy may be requested by the Investigator. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.5. Sponsor Reporting Requirements to Health Authorities and IRB/IEC

The Sponsor assumes responsibility for reporting of AEs including SUSARs according to local and international regulations, as appropriate. The Investigator (or the Sponsor where required) must report these events to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

13. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

The Sponsor of this study may delegate some administrative aspects of this study to a duly authorized representative including, but not limited to, study initiation, monitoring, and management of SAE reports.

13.1. Data Collection, Processing, and Monitoring

13.1.1. Case Report Forms and Source Documentation

All data captured for the study is planned to be electronic. However, if necessary, data captured may be performed using paper Case Report Forms (CRFs). The Investigator agrees to enter into the electronic data capture (EDC) system all data associated with a patient's study-related visit within 5 working days of that visit.

CRFs will be provided by the Sponsor or its representative and should be handled in accordance with the instructions provided by the Sponsor or designated representative.

The Investigator is responsible for maintaining adequate and accurate CRFs which have been designed to record all observations and other data pertinent to the clinical investigation. Each CRF should be filled out completely by the Investigator or delegate as stated in the Site Delegation List.

If paper CRFs are used, then all CRFs should be completed in a neat legible manner to ensure accurate interpretation of the data; a black ball-point pen should be used to ensure the clarity of reproduced copies of all CRFs. Incorrect entries should be crossed with a single line. Corrections must be made adjacent to the item to be altered, initialed and dated with the reason for the correction if necessary, by an authorized (Investigator/study team designee) person. Overwriting of this information or use of liquid correcting fluid is not allowed.

The data should be reviewed, signed and dated by the Investigator for accuracy and completeness. Once the site monitor has verified the contents of the completed CRF pages against the source data, queries may be raised if the data are unclear or contradictory. These queries must be addressed by the Investigator and verified by the clinical research associate within 5 days of receipt. After all the data issues are resolved, these CRFs may be locked to prevent any further data changes.

13.1.2. Study Monitoring and Access to Source Documentation

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of the US FDA, the European Medicines Agency (EMA), other national authorities, eg, the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), the German Federal Institute for Drugs and Medical Devices (BfArM), and local health authorities, the Sponsor and representatives, and the IRB/EC for each study site. The Investigator will permit authorized representatives of the Sponsor, the respective national or local health authorities, and auditors to inspect facilities and records relevant to this study.

The Sponsor or representative's monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research.

Source data to be reviewed during this study will include, but is not restricted to patient's medical file, patient's diary (if applicable), and original laboratory test, histology, and pathology reports. All key data must be recorded in the patient's hospital notes.

Auditors, IEC/IRB and/or regulatory inspectors will also have access to the CRFs and source documents. The ICF will include a statement by which the patient allows the monitor/auditor/inspector from the IEC/IRB or regulatory authority access to source data (eg, patient's medical file, appointment books, original laboratory test reports, X-rays, etc.) that substantiate information in the CRFs. These personnel, bound by professional secrecy, will not disclose any personal information or personal drug information.

13.1.3. Data Quality Assurance

In accordance with ICH E6 Good Clinical Practice (GCP) and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's (or designee's) Quality Assurance Department. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP (ICH E6), US Investigational Drugs (21CFR50, 54, 56, and 312), European Union (EU) Clinical Studies Directive (Directive 2001/20/EC), and applicable regional regulatory requirements.

The Sponsor's representatives are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that patient confidentiality is respected.

The Investigator agrees to cooperate with the Sponsor representative to ensure that any problems detected in the course of these inspection visits, including delays in completing CRFs, are resolved.

13.1.4. Data Processing

All data will be entered by site personnel into the electronic data capture system/CRF (as detailed in Section 13.1.1).

The data-review and data-handling document will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction sheets for unresolved queries will be sent to the study monitors for resolution with the Investigator. The database will be updated on the basis of signed corrections.

Previous and concomitant medications will be coded using the World Health Organization Drug Reference List (WHO Drug), which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history and AEs will be coded using the MedDRA terminology. The versions of the coding dictionaries will be provided in the Clinical Study Report.

13.1.5. Retention of Data and Study Records

As described in the ICH GCP Guidelines, 'essential documents', including CRFs, source documents, ICFs, laboratory test results, and drug inventory records, should be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or

at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Investigator should obtain written permission from the Sponsor prior to the destruction of any study document.

These records should be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with 21 CFR 312.68 or other National Regulatory Authorities.

13.2. Ethical Aspects

13.2.1. Good Clinical Practice and Ethical Conduct of the Study

This protocol accords with the principles of the Declaration of Helsinki as set forth at the 18th World Medicines Association (Declaration of Helsinki, 1964) and amendments thereto. The most current amended version will be in effect.

The procedures set out in this study protocol are also designed to ensure that the Sponsor and Investigator abide by the principles of the GCP guidelines of the ICH and in keeping with local legal requirements.

13.2.2. Informed Consent Responsibilities

It is the responsibility of the Investigator to obtain written informed consent from the patient or patient's legal representative. If informed consent has not been obtained, no protocol-required procedures are to be performed on the patient and no patient data are to be transferred to the Sponsor. Documentation of informed consent must be recorded in the source documents for each patient.

The study will be discussed with the patient, and the patient will receive written information and an explanation of what the study involves, ie, the objectives, potential benefits and risk, inconveniences, and the patient's rights and responsibilities. If applicable, the information will be provided in a certified translation of the local language.

A signed, IRB/IEC approved ICF must be obtained from the patient before any study specific procedures can occur. Confirmation of the patient's informed consent and the informed consent process must also be documented in the patient's medical record. Signed ICFs must remain in each patient's study file and must be available for verification by study monitors at any time. A copy of the fully signed ICFs will be given to the patient.

If the IEC/IRB requires modification of this form, the documentation supporting this requirement must be provided to the Sponsor, along with the new version. The Sponsor reserves the right to reject these modifications, should they not cover the minimum information required by ICH GCP.

A patient wishing to participate must also provide Authorization for Use and Release of Health and Research Study Information (US only) or Data Protection Consent (Europe only) prior to any study-related procedures or change in treatment.

If a patient is not physically or mentally competent to understand and to give their informed consent to participate in the study (eg, is blind or illiterate), a legally acceptable representative or

impartial witness as applicable, may sign the ICF on behalf of the patient. It remains the responsibility of the principal Investigator to assure that the patient is suitable for inclusion in this study and will be able to adhere to all study procedures throughout the course of the study.

The explicit wish of a minor or mentally incapacitated adult, who is capable of forming an opinion and assessing the study information, to refuse participation in or to be withdrawn from the study at any time will be respected by the Investigator.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

13.3. Other Study Administration Aspects

13.3.1. Protocol Approval and Protocol Amendment

The protocol (approved by the Sponsor or its representative) will be submitted to the IRB/IEC for review and it must be approved before the study is initiated. Prior to implementing changes in the study, the Sponsor will produce a protocol amendment and the IRB/IEC must also approve any amendments to the protocol.

Any change in the study plan requires a protocol amendment. An Investigator must not make any changes to the study without IRB/IEC and Sponsor approval except when necessary to eliminate apparent immediate hazards to the patients. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB/IEC within 5 working days, and submitted to the appropriate regulatory agency in the required time frame. All protocol amendments must be reviewed and approved by the Sponsor and the Investigator.

13.3.2. Investigator Responsibilities

The Investigator undertakes to perform the study in compliance with the protocol, ICH Guidelines per GCP and the applicable regulatory requirements. A copy of the guidelines will be available in the Investigator Site File.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the investigational site prior to commitment to participate in this study. The Investigator should also be able to demonstrate a potential for recruiting the required number of suitable patients within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. An up-to-date copy of the curriculum vitae for the Investigator and sub-Investigator(s) will be provided to the Sponsor (or its representative) before starting the study.

If the patient has a primary physician, the Investigator should, with the patient's consent, inform the primary physician of the patient's participation in the study.

Agreement with the final clinical study report will be documented by the signed and dated signature of the principal or coordinating Investigator in compliance with ICH E3.

The Investigator must adhere to the protocol as detailed in this document. The Investigator will be responsible for enrolling only those patients who have met protocol eligibility criteria. The Investigators will be required to sign an Investigator agreement to confirm acceptance and willingness to comply with the study protocol.

It is the Investigator's responsibility to communicate with their local IRB/IEC to ensure accurate and timely information is provided at all stages during the study. In particular, the appropriate approvals must be in place prior to recruitment, notification of any SAEs during the study must take place and the IRB/IEC must be informed of study completion.

It is the responsibility of the Investigator to submit this protocol, the final approved informed consent document (approved by the Sponsor or its representative), relevant supporting information, all types of patient recruitment or advertisement information (approved by the Sponsor or its representative), and all written materials provided to the study patients to the IRB/IEC for review; these must be approved before the study is initiated or use. Prior to implementing changes in the study, the Sponsor will produce a protocol amendment and the IRB/IEC must also approve any amendments to the protocol.

On the approval letter, the study (title, protocol number and version), the documents reviewed (protocol, informed consent material, amendments) and the date of review should be clearly stated.

Investigational product supplies will not be released, and the patient recruitment will not begin until this written approval has been received by the Sponsor or its designee.

The Investigator is responsible for keeping the IRB/IEC appraised of the progress of the study and of any changes made to the protocol as deemed appropriate, and at least once per year. The Investigator must also keep the IRB/IEC informed of any serious and significant AEs.

13.3.3. Patient Confidentiality

Data collected during this study may be used to support the development, registration or marketing of neratinib. All data collected during the study will be controlled by the Sponsor (or designee) and the Sponsor will abide by all relevant data protection laws. After a patient has consented to take part in the study, their medical records and the data collected during the study will be reviewed by representatives of the Sponsor and/or the company organizing the research on the Sponsor's behalf to confirm that the data collected are accurate and for the purpose of analyzing the results. These records and data may additionally be reviewed by auditors or by regulatory authorities. The patient's name, however, will not be disclosed outside the hospital. They will be known by a unique patient number. The results of this study may be used in other countries throughout the world that have ensured an adequate level of protection for personal data.

Written Authorization (US sites only) or Data Protection Consent (European sites only) is to be obtained from each patient prior to enrollment into the study, and/or from the patient 's legally authorized representative in accordance with the applicable privacy requirements [eg, the Health Insurance Portability and Accountability Act of 1996 Standards for Privacy of Individually Identifiable Health Information ("HIPAA"), European Union Data Protection Directive 95/46/EC ("EU Directive") and any other state and country privacy requirements]. If the patient is under the legal age of consent, the Authorization (US sites only) or Data Protection form

(European sites only) must be signed by the legally authorized representative in accordance with the applicable privacy requirements and other state and country privacy requirements.

13.3.4. Financial Disclosure

The Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the outcome of the study; any significant payments of other sorts from the Sponsor, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any proprietary interest in neratinib; any significant equity interest in the Sponsor, as defined in the US Code of Federal Regulations (21 CFR 54 2(b)).

In consideration of participation in the study, the Sponsor will pay the Investigator, study site or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

13.3.5. Publication Policy

The Sponsor encourages publication of results derived from the clinical research it sponsors. Publications include a paper in a peer reviewed medical journal, abstract submission with a poster or oral presentation at a scientific meeting or making results public by some other means. The Sponsor will retain the right to review all material prior to presentation or submission for publication and neither institution(s) nor Study Co-chairs/Principal Investigator(s) are permitted to publish/present the results of the study, in part or in their entirety, without the written authorization of the Sponsor. The review is aimed at protecting the Sponsor's pre-existing proprietary information and commercial interests.

In all publications, the study is to be identified as PUMA-NER-5201. The Study Principal Investigator(s) shall be free to publish or present, subject to the timing described in the Clinical Study Agreement.

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15. SIGNATURE PAGES

Declaration of Sponsor or Responsible Medical Officer

Title: An Open-Label, Phase 2 Basket Study of Neratinib in Patients With Solid Tumors With Somatic Activating *HER* Mutations

Study Number: PUMA-NER-5201

I have read and approve this protocol. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws, regulations, and guidelines, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the United States Code of Federal Regulations (CFR), the Directives of the European Union, the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

[redacted]

[redacted] 10-Feb-2021 | 12:43 PST

Name Date

[redacted]

Title

Declaration of Principal Investigator

Title: An Open-Label, Phase 2 Basket Study of Neratinib in Patients With Solid Tumors With Somatic Activating *HER* Mutations

Study Number: PUMA-NER-5201

I have read and approve this protocol. My signature, in conjunction with the signature of the Sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws, regulations, and guidelines, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the United States Code of Federal Regulations (CFR), the Directives of the European Union, the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the patients.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

_____
Signature

_____ _____
Name Date

_____ _____
Title Institution (block letters)

_____ _____
Address Phone number

16. APPENDICES

APPENDIX 1 SCHEDULE OF PROCEDURES

Table A1.1. Schedule of Study Procedures for Cohorts Receiving Trastuzumab Combination Therapy

Event	Screening		Treatment														Follow-up[b]
Visit			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5		
Study Week			W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	EOT[a]	
Cycle Day	Within 28 days of C1D1	Within 14 days of C1D1	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1		
Informed consent	X																
Demographics		X															
Medical, cancer, and medication history[c]		X															
Physical examination[d]/vital signs[d]		X	X[e]			X			X			X			X	X	
Electrocardiogram		X														X	
ECHO/MUGA[f]	X														X[f]	X	
Urine test[g]/ Pregnancy test[g]		X															
Hematology[h] / Serum chemistry panel[h]		X	X[i]			X			X			X			X	X	
Plasma collection for cfDNA biomarker analysis[j]		X[j]										X[j]				X[j]	
Whole blood sample for germline DNA[k]		X															
ECOG status		X	X[e]			X			X			X			X		
Neratinib[l]			X														
Trastuzumab[l]			X			X			X			X			X		
Fulvestrant[l]			X		X		X				X				X		
Tumor evaluation[m]	X[m]											X[m]				X[m]	X[m]
MD/RN Phone call[n]			X[n]														X[o]
Mandatory fresh pretreatment tumor biopsy for all breast cancer patients	X																
Archival and/or fresh pretreatment metastatic tumor tissue sample for all patients	X[p]																
Optional on-treatment or end-of-treatment fresh core tumor biopsy[q]											X[q]					X[q]	
Loperamide antidiarrheal treatment[r]			Administered orally daily						Administered orally as needed (not to exceed 16 mg per day)								
Patient Diary[s]			X														
Concomitant therapy	Collected continuously throughout study period																
Adverse events[t]	Collected continuously throughout study period																
Patient Reported Outcomes[u]	X[u]		X[u]			X[u]			X[u]			X[u]			X[u]	X[u]	

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; cfDNA = cell-fee DNA; CT = computerized tomography; D = Day; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FFPE = formalin-fixed paraffin embedded; Hb = hemoglobin; Hct = hematocrit; ICF = informed consent form; IP = Investigational Product; LDH = lactate dehydrogenase; MD = medical doctor; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition scan; PD = progressive disease; PET = positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumors; RBC = red blood cells; RN = registered nurse; W = week; WBC = white blood cell

a. EOT follow-up assessments will be conducted 28 days (+14 days) after the last administration of IP(s). AEs must be followed for 28 days after the last administration of IP(s).
b. Follow-up visits will occur every 3 cycles (9 weeks ±7 days) for patients discontinuing treatment for any reason other than disease progression until objective disease progression is reported per RECIST v 1.1 (or other response criteria). After disease progression, all patients will be followed every 12 weeks for survival and anti-cancer medication taken will be recorded.
c. Collect chronic medical condition and medical history of significance (including smoking history only for lung cancer patients), or symptoms experienced during the previous 30 days and those ongoing at the time of screening, and any medical conditions that require medication. Identify start of current medical conditions by at least providing the year of onset.
d. Physical examination may be delegated and performed by a properly trained nurse practitioner, physician's assistant, or equivalent. Full physical examination at screening, C1D1, and thereafter should be a detailed/brief (system-guided) physical examination to evaluate any clinically significant abnormalities; including worsening of medical history conditions. Vital signs include pulse, blood pressure, temperature (in Celsius) and respiration rate taken before dosing. Also includes height (screening only) and weight.
e. Physical examination / ECOG status does not need to be repeated if performed within 72 hours prior to C1D1.
f. Patients treated with neratinib in combination with trastuzumab will have ECHO/MUGAs performed at baseline, at the beginning of Week 13, every 4 cycles (12 weeks ± 7 days) thereafter, at EOT, and every 6 months up to 24 months after the last dose of trastuzumb.
g. Laboratory urinalysis or by urine dipstick (blood, protein, glucose, and microscopic examination, if abnormal). Urine or serum pregnancy test only for women of child-bearing potential (at screening, and to be repeated only if performed outside 72 hours of C1D1).
h. Hematology panel: Hct, Hb, platelet count, RBC count, and WBC count with differential. Serum chemistry: albumin, alkaline phosphatase, ALT, AST, BUN, calcium, chloride, serum creatinine, glucose (non-fasting), LDH, magnesium, phosphorous, potassium, serum cholesterol (non-fasting), total bilirubin, total protein, and sodium. Following C1, laboratory tests may take place ± 2 days before Day 1.
i. Laboratory assessments are not required on C1D1 if previously obtained within 72 hours prior to C1D1 as part of screening, with no clinically significant findings.
j. Plasma collection for cfDNA biomarker analysis at screening (if collected on C1D1, it has to be done prior to the first IP dose), at the beginning of Week 10 (ORR_{first}), and every 3 cycles (9 weeks ± 7 days) thereafter, and during the EOT visit.
k. Whole blood sample for research (single collection) obtained during study, preferably during screening or within the first cycle of therapy.
l. Neratinib, trastuzumab, and fulvestrant administration performed as described in Section 5.1. Following C1, fulvestrant administration may take place ± 2 days.
m. Tumor assessment at screening should occur within 4 weeks of C1D1, as appropriate. Post-treatment disease assessment by CT or PET/CT scan or MRI of the chest, abdomen and pelvis, as appropriate, will be conducted at the beginning of Week 10 (ORR_{first}), every 3 cycles (9 weeks ± 7 days) thereafter until 1 year and annually (once per year). Following one year on therapy, scans may move to every 4 cycles for trastuzumab-containing regimens. Following two years on therapy, scans may move to every 5 cycles for trastuzumab-containing regimens. The scans must be obtained and reviewed prior to start of the next cycle. CT or PET/CT or MRI should be done only at EOT if not done within the previous 4 weeks, or if required to confirm an objective response. Overall response will be scored by independent assessment and by the Investigator per RECIST v1.1 using the algorithms defined in the protocol. Tumor assessments should be continued every 3 cycles (9 weeks ± 7 days) for any patients ending therapy for any reason other than radiological PD. Patients with a history of brain metastases or those symptomatic for brain metastases will have a brain CT or MRI at baseline. For patients who enrolled prior to Amendment 6, the same method of measurement (eg PET/CT) and same method of disease assessment (eg metabolic response by PET Response Criteria) should continue through final assessments.
n. Phone call to patient 1 day, 2 days, and 3 days after the first dose of neratinib (C1D1) to check on diarrhea symptoms and patient compliance with anti-diarrheal therapy.
o. AEs, SAEs, and clinically significant abnormal laboratory results should be followed for 28 days after the last dose of IP(s); this information may be collected at the EOT visit or via phone call. Follow patients via phone call every 12 weeks (±14 days) after disease progression to monitor survival.
p. Archival tissue sample obtained during screening or within the first cycle of therapy. In cases where a patient is enrolled based on a documented *HER* mutation derived from a cfDNA specimen (ie, liquid biopsy), a mandatory archival FFPE or fresh-tumor biopsy should be submitted for retrospective central confirmation of the mutation.
q. Optional fresh core tumor biopsy from all patients upon progression of disease.
r. Loperamide antidiarrheal treatment should be dispensed with the initial supply of neratinib. All patients taking neratinib will maintain a patient diary for the study to record each dose of neratinib taken and while receiving antidiarrheal prophylaxis with loperamide taken for the first two cycles of treatment.
s. Patient Diary will be provided by the Investigator for the patient to record daily study medication intake for every cycle, and frequency and management of diarrhea in the first 2 cycles.

[t.] Symptoms should be assessed from signing of ICF and during any protocol visit that includes a physical examination. AEs should be followed for 28 days after last administration of IP(s).
[u.] FACT-G will be performed at Screening, C1D1 and at the beginning of each cycle for up to 6 months or EOT, whichever comes first.

Table A1.2. Schedule of Study Procedures for Cohorts Not Receiving Trastuzumab

Event	Screening		Treatment														Follow-up[b]
Visit			Cycle 1				Cycle 2				Cycle 3				Cycle 4		
Study Week			W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	EOT[a]	
Cycle Day	Within 28 days of C1D1	Within 14 days of C1D1	D1	D8	D15	D22	D1	D8	D15	D22	D1	D8	D15	D22	D1		
Informed consent	X																
Demographics		X															
Medical, cancer, and medication history[c]		X															
Physical examination[d]/vital signs[d]		X	X[e]				X				X				X	X	
Electrocardiogram[f]		X													X[f]	X	
ECHO/MUGA	X															X	
Urine test[g]/ Pregnancy test[g]		X															
Hematology[h] / Serum chemistry panel[h]		X	X[i]				X				X				X	X	
Plasma collection for cfDNA biomarker analysis[j]		X[j]									X[j]					X[j]	
Whole blood sample for germline DNA[k]		X															
ECOG status		X	X[e]				X				X				X		
Neratinib[l]			X														
Fulvestrant[l]			X		X		X				X				X		
Tumor evaluation[m]	X[m]										X[m]					X[m]	X[m]
MD/RN Phone call[n]			X[n]														X[o]
Mandatory fresh pretreatment tumor biopsy for all breast cancer and NSCLC patients	X																
Most recent metastatic tumor tissue sample for all patients	X[p]																
Optional on-treatment or end-of-treatment fresh core tumor biopsy[q]											X[q]					X[q]	
Loperamide antidiarrheal treatment[r]			Administered orally daily								Administered orally as needed (not to exceed 16 mg per day)						
Patient Diary[s]			X														
Concomitant therapy	Collected continuously throughout study period																
Adverse events[t]	Collected continuously throughout study period																
Patient Reported Outcomes[u]	X[u]		X[u]				X[u]				X[u]				X[u]	X[u]	

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; cfDNA = cell-fee DNA; CT = computerized tomography; D = Day; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FFPE = formalin-fixed paraffin embedded; Hb = hemoglobin; Hct = hematocrit;

ICF = informed consent form; IP = Investigational Product; LDH = lactate dehydrogenase; MD = medical doctor; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition scan; NSCLC = non-small cell lung cancer; PD = progressive disease; PET = positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumors; RBC = red blood cells; RN = registered nurse; W = week; WBC = white blood cell

a. End of treatment (EOT) follow-up assessments will be conducted 28 days (+14 days) after last administration of IP(s). AEs must be followed for 28 days after last administration of IP(s).
b. Follow-up visits will occur every 2 cycles (8 weeks ± 7 days) for patients discontinuing treatment for any reason other than disease progression until objective disease progression is reported per RECIST v 1.1 (or other response criteria). After disease progression, all patients will be followed every 12 weeks for survival and anticancer medication taken will be collected.
c. Collect chronic medical condition and medical history of significance (including smoking history only for lung cancer patients), or symptoms experienced during the previous 30 days and those ongoing at the time of screening, and any medical conditions that require medication. Identify start of current medical conditions by at least providing the year of onset.
d. Physical examination may be delegated and performed by a properly trained nurse practitioner, physician's assistant, or equivalent. Full physical examination at screening, C1D1 and thereafter should be a detailed/brief (system-guided) physical examination to evaluate any clinically significant abnormalities; including worsening of medical history conditions. Vital signs include pulse, blood pressure, temperature (in Celsius) and respiration rate taken before dosing. Also includes height (screening only) and weight.
e. Physical examination / ECOG status does not need to be repeated if performed within 72 hours prior to C1D1.
f. All neratinib monotherapy cohorts will have ECGs performed at baseline and at end of treatment only.
g. Laboratory urinalysis or by urine dipstick (blood, protein, glucose, and microscopic examination, if abnormal). Urine or serum pregnancy test only for women of child-bearing potential (at screening, and to be repeated only if performed outside 72 hours of C1D1).
h. Hematology panel: Hct, Hb, platelet count, RBC count, and WBC count with differential. Serum chemistry: albumin, alkaline phosphatase, ALT, AST, BUN, calcium, chloride, serum creatinine, glucose (non-fasting), LDH, magnesium, phosphorous, potassium, serum cholesterol (non-fasting), total bilirubin, total protein, and sodium. Following C1, laboratory tests may take place ± 2 days before Day 1.
i. Laboratory assessments are not required on C1D1 if previously obtained within 72 hours prior to C1D1 as part of screening, with no clinically significant findings.
j. Plasma collection for cfDNA biomarker analysis at screening (if collected on C1D1, it has to be done prior to the first IP dose), at the beginning of Week 9 (ORR_{first}), and every 2 cycles (8 weeks ± 7 days) thereafter, and during the EOT visit.
k. Whole blood sample for research (single collection) obtained during study, preferably during screening or within the first cycle of therapy.
l. Neratinib and fulvestrant administration performed as described in Section 5.1.
m. Tumor assessment at screening should occur within 4 weeks of C1D1, as appropriate. Post-treatment disease assessment by CT or PET/CT scan or MRI of the chest, abdomen and pelvis, as appropriate, will be conducted at the beginning of Week 9 (ORR_{first}), and every 2 cycles (8 weeks ± 7 days) until 1 year, and annually (once per year). Following one year on therapy, scans may move to every 3 cycles for non-trastuzumab containing regimens. Following two years on therapy, scans may move to every 4 cycles for non-trastuzumab containing regimens. The scans must be obtained and reviewed prior to start of the next cycle. CT or PET/CT or MRI should be done only at EOT if not done within the previous 4 weeks, or if required to confirm an objective response. Overall response will be scored by independent assessment and by the Investigator according to RECIST v1.1 using the algorithms defined in the protocol. Tumor assessments should be continued every 2 cycles (8 weeks ± 7 days) for any patients ending therapy for any reason other than radiological PD. For patients who enrolled prior to Amendment 6, the same method of measurement (eg PET/CT) and same method of disease assessment (eg metabolic response by PET Response Criteria) should continue through final assessments.
n. Phone call to patient 1 day, 2 days, and 3 days after the first dose of neratinib (C1D1) to check on diarrhea symptoms and patient compliance with anti-diarrheal therapy.
o. AEs, SAEs, and clinically significant abnormal laboratory results should be followed for 28 days after the last dose of IP(s); this information may be collected at the EOT visit or via phone call. Follow patients via phone call every 12 weeks (±14 days) after disease progression to monitor survival.
p. Archival tissue sample obtained during screening or within the first cycle of therapy. In cases where a patient is enrolled based on a documented *HER* mutation derived from a cfDNA specimen (ie, liquid biopsy), a mandatory archival FFPE or fresh-tumor biopsy should be submitted for retrospective central confirmation of the mutation.
q. Optional fresh core tumor biopsy from all patients upon progression of disease.
r. Loperamide antidiarrheal treatment should be dispensed with the initial supply of neratinib. All patients taking neratinib will maintain a patient diary for the study to record each dose of neratinib taken and while receiving antidiarrheal prophylaxis with loperamide taken for the first two cycles of treatment.
s. Patient Diary will be provided by the Investigator for the patient to record daily study medication intake for every cycle, and frequency and management of diarrhea in the first 2 cycles.
t. Symptoms should be assessed from signing of ICF and during any protocol visit that includes a physical examination. AEs should be followed for 28 days after last administration of IP(s).
u. FACT-G will be performed at Screening, C1D1 and at the beginning of each cycle for up to 6 months or EOT, whichever comes first.

APPENDIX 2 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

APPENDIX 3 INHIBITORS AND INDUCERS OF THE CYTOCHROME P450 ISOENZYMES

CYP3A4 Inducers		
Carbamazepine	Macrolide Antibiotics	Rifabutin
Efavirenz	Phenobarbital	Rifampin
Glucocorticoids	Phenylbutazone	Rifapentine
Dexamethasone	Phenytoin	Sulfinpyrazone
Prednisone	Primidone	
CYP3A4 Inhibitors		
Amprenavir	Grapefruit Juice	Propranolol
Anastrozole	Indinavir	Quinine
Cimetidine	Itraconazole	Quinidine
Clarithromycin	Ketoconazole	Ranitidine
Clotrimazole	Mibefradil	Ritonavir
Danazol	Miconazole	Saquinavir
Delavirdine	Mirtazapine (weak)	Sertraline
Diethyldithiocarbamate	Nefazodone	Sildenafil (weak)
Diltiazem	Nelfinavir	Troglitazone
Erythromycin	Nevirapine	Troleandomycin
Fluconazole	Norfloxacin	Zafirlukast
Fluoxetine	Norfluoxetine	
Fluvoxamine	Paroxetine	
CYP3A5-7 Inducers		
Phenobarbital	Primidone	Rifampin
Phenytoin		
CYP3A5-7 Inhibitors		
Clotrimazole	Metronidazole	Troleandomycin
Ketoconazole	Miconazole	

APPENDIX 3. INHIBITORS AND INDUCERS OF THE CYTOCHROME P460 ISOENZYMES (CONTINUED)

CYP2D6 Substrate		
Carvedilol	Maprotiline	Selegiline
Chloroquine (possible)	Methamphetamine	Sertraline
Chlorpromazine	Metoprolol	Sparteine
Citalopram	Mexiletine (major)	Tamoxifen
Clozapine	Mirtazapine	Thioridazine
Codeine	Morphine	Timolol
Cyclobenzaprine	Olanzapine	Tolterodine (major)
Debrisoquin	Ondansetron	Tramadol
Delavirdine	Oxaminiquine	Trazodone
Dexfenfluramine	Oxycodone	TCAs (hydroxylation)
Dextromethorphan	Paroxetine	Amitriptyline
Dolasetron	Penbutolol	Clomipramine
Donepezil	Pentazocine	Desipramine
Encainide	Perphenazine	Doxepin
Flecainide	Phenformin	Imipramine
Fluoxetine	Primaquine (possible)	Nortriptyline
Fluphenazine	Propafenone	Trimipramine
Halofantrine	Propoxyphene	Venlafaxine
Haloperidol	Propranolol (minor)	Ziprasidone
Hydrocodone	Risperidone	Zolpidem
Hydroxyamphetamine	Ritonavir	
Labetalol	Ropivacaine	

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

APPENDIX 4 SUBSTRATES AND INHIBITORS OF P-GLYCOPROTEIN (P-GP)

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)	

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

APPENDIX 5 DRUGS ASSOCIATED WITH RISK OF QT/QTC PROLONGATION LEADING TO TORSADE DE POINTES

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

Drugs Reported to Prolong QT Interval		
Calcium channel blockers		
Isradipine (DynaCirc)	Nicardipine (eg, Cardene)	
Contrast media		
Ionic contrast media*	Non-ionic contrast media: Iohexol (Omnipaque)	
Corticosteroids		
Prednisolone (eg, Prelone)	Prednisone (eg, Deltasone)*	
Diuretics		
Furosemide (eg, Lasix)	Indapamide (eg, Lozol)	
Gastrointestinal agents		
Cisapride (Propulsid)*[b]	Famotidine (eg, Pepcid)*	
Immunosuppressants		
Tacrolimus (Protopic)*[b] (postmarketing)		
Miscellaneous		
Levomethadyl	Papaverine (eg, Pavaden three times daily [TID])*	
Moexipril/Hydrochlorothiazide (Uniretic)	Probucol (Lorelco)*	
Octreotide (Sandostatin)[b]	Vasopressin (eg, Pitressin)*	
Oxytocin (eg, Pitocin; IV bolus)		
Psychotropics		
Droperidol (eg, Inapsine)*	Primozide (Orap)*[b]	Trazodone (eg, Desyrel)
Haloperidol (eg, Haldol)*	Quetiapine (Seroquel)[b]	Tricyclic antidepressants
Lithium (eg, Eskalith)*	Risperidone (Risperdal)[b] (overdose)	Amitriptyline*
Maprotiline*	Serotonin Reuptake Inhibitors (SRIs)	Clomipramine (eg, Anafranil)
Phenothiazines	Citalopram (eg, Celexa)*	Desipramine (eg, Norpramin)*
Chlorpromazine (eg, Thorazine)*	Fluoxetine (eg, Prozac)*[a]	Doxepin (eg, Sinequan)*
Fluphenazine (eg, Prolixin)*	Paroxetine (eg, Paxil)*	Imipramine (eg, Tofranil)*
Perphenazine	Sertraline (Zoloft)*[a, b] (postmarketing)	Nortriptyline (eg, Pamelor)
Thioridazine (Mellaril)*[b]	Venlafaxine (Effexor)[b] (postmarketing)	
Trifluopherazine		
Serotonin 5-HT[1] agonists		
Naratriptan (Amerge)	Sumatriptan (Imitrex)[b]	Zolmitriptan (Zomig)[b]
Skeletal muscle relaxants		
Tizanidine (eg, Zanaflex)[b] (animals)		

* Drugs 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 Interaction Facts: The Authority on Drug Interactions. Wolters Kluwer Health, 2012.

APPENDIX 6 RECIST V1.1 CRITERIA

Patient Eligibility

Only patients with measurable disease at baseline should be included in this study. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criterion.

Note: Lesions are either measurable or nonmeasurable using the criteria provided below. The term "evaluable" in reference to measurability provides neither additional meaning nor accuracy and will not be used.

Measurable Disease

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

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

Nonmeasurable Disease

- Small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis).
- Truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For

example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days before the beginning of the treatment.

Method of assessment

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

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

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

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

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

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

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

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of nontarget lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions.

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD (stable disease): Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression).

Table A6.1. Evaluation Criteria

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	SD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR: complete response; NE: not evaluated; PD: progressive disease; PR: partial response; SD: stable disease.

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

Confirmatory Measurement/Duration of Response

Confirmation

In nonrandomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, ie, in randomized studies (phase 2 or 3) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not

blinded. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (not less than 6 weeks) that is defined in the study protocol.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of patients achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between two measurements for determination of SD. Note: The DOR and SD as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

Optimal duration of treatment with hormone therapy

Treatment should be administered until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms. Tumor markers or circulating tumor cells should not be used as the sole criteria for determining progression.

Assessment of progression may be challenging because of the combination of difficulty in interpreting imaging and the indolent nature of HR+ disease in some patients. Treatment should focus on patient outcomes and symptoms. Tumor flare reactions (increase in tumor-related symptoms) can occur, particularly with tamoxifen and estradiol; were observed shortly after beginning a new endocrine treatment; and can be confused with disease progression. Treatment-related toxicity may be a reason to change therapy Patient outcomes were not improved by changing therapy based solely on tumor markers or circulating tumor cells.

Sources: Boellaard, et al, 2010; Brucher et al, 2001; Costelloe et al 2009; Costelloe, et al; 2010; Dose Schwarz et al, 2005; Gayed et al, 2004; Hawkins et al 2009; Hellwig et al, 2004; Mac Manus et al, 2003; Rugo, et al; 2016; Shankar, et al; 2006; Smith et al, 2000; Stroobants et al, 2003; Swisher et al, 2004; Van den Abbeele et al, 2008; Wahl, et al; 2009; Weber et al, 2006; Wieder et al, 2004; Young, et al; 1999

APPENDIX 7 SPECIFIC GUIDANCE ON *EGFR* AND *ERBB2* MUTATIONS

In the context of this study, the word *mutation* refers to an alteration of somatic, tumor-associated genomic DNA sequence that alters the protein coding region in a nonconserved manner, and may range from single base point mutations to larger regions of inserted, repeated or deleted genomic DNA sequence.

A list of known activating or potentially activating somatic mutations in *ERBB2* is provided in Table A7.1 and in *EGFR* exon 18 in Table A.7.2. The mutations in this list have been characterized in the scientific literature (PubMed) and/or identified in two or more cases as detailed in publicly available databases (COSMIC, cBioPortal for Cancer Genomics).

In cases where a patient is enrolled based on a documented *ERBB* mutation derived from a cfDNA specimen (ie, liquid biopsy), a mandatory archival FFPE or fresh-tumor biopsy should be submitted for retrospective central confirmation of the mutation.

Table A7.1. Eligible *ERBB2* Mutations

1 Letter Amino Acid Nomenclature	3 Letter Amino Acid Nomenclature	Other Common Nomenclature
G309A	Gly309Ala	
G309E	Gly309Glu	
S310F	Ser310Phe	
S310Y	Ser310Tyr	
S653C	Ser635Cys	
V659E	Val659Glu	
G660D	Gly660Asp	
V697L	Val697Leu	
T733I	Thr733Ile	
L755S	Leu755Ser	
L755P	Leu755Pro	
L755_T759del	Leu755_Thr759del	ΔLRENT
I767M	Ile767Met	
D769Y	Asp769Tyr	
D769H	Asp769His	
D769N	Asp769Asn	
Y772_A775dup	Tyr772_Ala755dup	A775_G776insYVMA
G776C	Gly776Cys	
G776V	Gly776Val	
G776VinsC/VGC/other	Gly776insCys/other	
Other exon 20 insertions		
V777L	Val777Leu	
G778_P780dup	Gly778_Pro780dup	P780_Y781insGSP
L841V	Leu841Val	
V842I	Val842Ile	
L869R	Leu869Arg	
L866M	Leu869Met	
H878Y	His878Tyr	
R896C	Arg896Cys	

Table A7.2. Eligible *EGFR* exon 18 Mutations

***EGFR* exon 18**
E709X
E709 indel
G719X
G719 indel

APPENDIX 8 PATIENT-REPORTED HEALTH OUTCOMES ASSESSMENT (FACT-G):

FACT-G (Version 4)

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

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

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4