AN OPEN-LABEL, PHASE 2 STUDY OF NERATINIB IN PATIENTS WITH SOLID TUMORS WITH SOMATIC HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR (*EGFR, HER2, HER3*) MUTATIONS OR *EGFR* GENE AMPLIFICATION

Study Protocol Number:	PUMA-NER-5201 (SUMMIT)
Disease Condition:	Solid tumors harboring somatic *ERBB* (*EGFR, ERBB2, ERBB3*) mutations or *EGFR* gene amplifications
Sponsor's Investigational Product Name/Formulation:	Neratinib Tablets

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CONFIDENTIALITY STATEMENT

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1. SELECTION OF PATIENTS, INCLUDING ELIGIBILITY AND INELIGIBILITY CRITERIA

1.1. 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.

1.2. Inclusion Criteria

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

Inclusion Criteria for All Patients:

1. Men and women who are ≥18 years old at signing of informed consent.
2. Histologically confirmed cancers in patients with activating *ERBB* mutations and/or *EGFR* amplification and who are refractory to standard therapy or for which standard or curative therapy does not exist or is not considered sufficient or appropriate by the Investigator.
3. At the time of screening, a previously documented mutation:
   i. *ERBB2* mutation in breast, bladder/urinary tract, biliary tract, colorectal, endometrial, gastroesophageal, lung, ovarian, and any other cancers, or
   ii. *EGFR* mutation/amplification in a primary brain tumor, or
   iii. *ERBB3* mutation in any cancer.
4. At least one measurable lesion, preferably as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1; Eisenhauer et al, 2009). Patients without RECIST measurable disease may be eligible for enrollment provided their disease can be evaluated for response using another accepted criteria (e.g. Gynecologic Cancer InterGroup [GCIG] CA125 Response Criteria [Rustin et al, 2011], Prostate Cancer Clinical Trials Working Group 2 (PCWG2) Criteria [Scher et al, 2008]; PET Response Criteria).
5. Left ventricular ejection fraction (LVEF) ≥50% measured by multiple-gated acquisition scan (MUGA) or echocardiogram (ECHO).
6. Eastern Cooperative Oncology Group (ECOG) status of 0-2.
7. Female patients with cancers known to secrete β-human chorionic gonadotropin (hCG), i.e. germinomas, are eligible if the pattern of serum β-hCG is suggestive of the malignancy and the pelvic ultrasound is negative for pregnancy.
8. Men must agree and commit to use a barrier method of contraception while on treatment and for 3 months after the last dose of the IP. Women of child-bearing potential must agree and commit to the use of a highly effective double-barrier method of contraception (e.g., 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. 6 months after the last dose of paclitaxel, or
iii. 1 year after the last dose of fulvestrant.

9. Provide written, informed consent to participate in the study and follow the study procedures.
10. A biomarker request form for the patient's mutation has been signed and approved for eligibility by the Sponsor.

Additional Inclusion Criteria for Breast Cancer Patients with Tumors that Harbor *ERBB2* Mutations

Both HR negative and HR positive cohorts

11. Must provide a pretreatment fresh biopsy within 28 days of starting treatment for all breast cancer patients unless the biopsy procedure presents a safety concern for the patient as determined by the Investigator.

HR positive cohort only

12. HR positive disease defined as ≥1% ER positive and/or PR positive cells (performed on the most recent biopsy as assessed locally and consistent with current ASCO/CAP or ESMO guidelines):
    i. Biopsy from a non-bony metastatic site: preferred, or
    ii. 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:
    i. Age ≥60 years;
    ii. 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 FSH level within the laboratory's reference range for postmenopausal females;
    iii. Documented bilateral oophorectomy,
    iv. Medically confirmed ovarian failure

OR

14. Pre/perimenopausal, i.e., not meeting the criteria for being postmenopausal:
    i. Pre/perimenopausal women can be enrolled if amenable to be treated with the LHRH agonist goserelin. Patients must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to randomization. But, if patients have received an alternative LHRH agonist prior to study entry, they must switch to goserelin for the duration of the trial
15. Documented disease progression after any prior chemotherapy or hormonal therapy (including fulvestrant).

Additional Inclusion Criteria for Patients with Primary Brain Tumors that Harbor *EGFR* Mutations (closed to enrollment in Amendment 4)

16. Have a diagnosis of glioblastoma multiforme (GBM), glioma (Grade III), gliosarcoma (Louis et al, 2007).
17. Has received prior treatment including radiation and/or chemotherapy.
18. Has documentation of *EGFR* gene amplification, *EGFR* mutation, or *EGFRvIII* deletion from most recent tumor sample.
19. Able to undergo repeated magnetic resonance imaging (MRI) scans.
20. Include patients with recurrent disease (confirmed by MRI and measurable by Macdonald criteria [Macdonald et al, 1990; Wen et al, 2010]) at the time of first or second recurrence or progression following initial definitive therapy(s) such as surgery with or without adjuvant radiation therapy and/or chemotherapy.
21. Have ≥1 site of bi-dimensionally measurable disease:
    i. The size of at least one of the measurable lesions should be ≥1 cm in each dimension and noted on more than one imaging slice.
    ii. Measured using contrast-enhanced MRI clearly limited residual lesion (re-growth within the surgical or irradiated field is acceptable).
    iii. Imaging study performed within 14 days before enrollment while on stable dose steroid medication for at least 5 days immediately before and during the imaging study.
22. Can provide 2 retrospectively collected pretreatment MRI scans (for evaluation of tumor growth dynamics).

1.3. Exclusion Criteria

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

Exclusion Criteria for All Patients:

1. Prior treatment with any *ERBB2*-directed TKI (e.g., lapatinib, afatinib, dacomitinib, neratinib) with the exception of NSCLC patients who may have received afatinib and remain eligible.
2. Not recovered to at least Grade 1 or baseline (CTCAE version 4.0) from all clinically significant AEs related to prior therapies (excluding alopecia).
3. Received chemotherapy or biologic therapy ≤2 weeks or 5 half-lives ($t_{½}$) of the agent used, whichever is shorter, prior to the start of neratinib.
4. Received radiation therapy ≤14 days prior to initiation of IP, except primary brain tumor patients.
5. 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, prostate or gynecological cancers.

6. 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.
7. Symptomatic or unstable brain metastases. (Note: Asymptomatic patients with metastatic brain disease who have been on a stable dose of corticosteroids for treatment of brain metastases for at least 14 days are eligible to participate in the study.) Patients with primary central nervous system tumors are eligible.
8. 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). For patients with NSCLC, the following are additionally excluded: conduction abnormality requiring a pacemaker; supraventricular and/or nodal arrhythmias not controlled with medication; valvular disease with documented compromise in cardiac function; symptomatic pericarditis; any history of myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LV function; any history of documented congestive heart failure (CHF) and/or cardiomyopathy.
9. 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).
10. Inadequate bone marrow, renal or hepatic function as defined on screening laboratory assessments outside the following limits:

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 baseline
Total bilirubin	>1.5 x institutional ULN (in case of known Gilbert's syndrome, >2 x 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 calculated by Cockroft-Gault formula[a] or Modification of Diet in Renal Disease [MDRD] formula[b])

a. Cockroft and Gault, 1976.
b. Levey et al, 1999.

11. Uncontrolled concurrent malignancy (early stage or chronic disease is allowed if not requiring active therapy or intervention and is under control).
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 (e.g., Crohn's disease, malabsorption, or Grade ≥2 National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events Version 4.0 [CTCAE v.4.0] diarrhea of any etiology at baseline).
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 IP, required combination therapy, or loperamide.
18. Unable or unwilling to swallow tablets.
19. Patients bearing certain somatic *ERBB* mutations, such as those that are subclonal in nature, or resulting in the expression of truncated proteins including alterations that result in a premature stop codon or a change in reading frame (i.e., frame shift mutations) may not be considered for eligibility.
20. Patients with known activating *KRAS* mutations.

Additional Exclusion Criteria for Patients with *ERBB2* Mutant Bladder/Urinary Tract Tumors for Combination Therapy Cohort

21. Prior progression after taxane therapy for metastatic bladder/urinary tract cancer.
22. Known hypersensitivity to paclitaxel (Taxol) or products containing Cremophor EL (polyoxyethylated castor oil).
23. Pre-existing Grade 2 or greater motor or sensory neuropathy.

Additional Exclusion Criteria for Patients with Primary Brain Tumors that Harbor *EGFR* Mutations (closed to enrollment in Amendment 4)

24. Prior or scheduled Gliadel® wafer implant unless area of assessment is outside the region previously implanted.
25. Prior interstitial brachytherapy or stereotactic radiosurgery unless area of assessment is outside the region previously treated.
26. Has received enzyme-inducing anti-epileptic drugs (EIAED) such as carbamazepine, phenytoin, phenobarbital, or primidone within 14 days before C1D1.
27. Received treatment with bevacizumab or any other anti-EGFR therapy (e.g., erlotinib, gefitinib, cetuximab, rindopepimut [CDX-110], etc.).
28. Received radiation therapy ≤12 weeks prior to initiation of investigational product.

Additional Exclusion Criteria for Patients with Colorectal Cancer (closed to enrollment in Amendment 4)

29. Patients with colorectal cancer with known activating *KRAS*, *BRAF*, or *NRAS* mutations.

1.4. Cohort Assignment

Patients will be assigned to cohorts based on tumors harboring somatic mutations in *EGFR*, *ERBB2*, or *ERBB3*, or tumors that have *EGFR* amplification, identified through previously documented mutation testing performed prior to screening and by the tumor type. If a tumor harbors more than one qualifying aberration/mutation, then the patient will be assigned to the appropriate tumor-specific cohort, if it exists, upon consultation with the Investigator and Sponsor.

Mutation/overexpression status of a tumor should be documented using molecular assays available at study sites.

2. SCHEMA AND TREATMENT PLAN, INCLUDING ADMINISTRATION SCHEDULE

2.1. Schema

No schema is available for this study.

2.2. Tumor Cohorts

Neratinib will be administered orally with food once daily (recommended to be taken in the morning), on a continuous basis. All patients will maintain a patient diary for the study to record each dose of neratinib taken and for the first required cycle of loperamide. Patients will undergo radiographic evaluation of their disease every 2 cycles (except for brain cancer patients who will undergo this assessment at 4 weeks and every 8 weeks thereafter). Survival follow-up will be every 12 weeks after treatment discontinuation. 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. In RECIST evaluable patients, an isolated metabolic progression will not necessarily trigger changes in therapy. Enrollment will continue as dictated by the Simon 2-stage design in all the histology and mutation specific cohorts and/or up to 30 patients per cohort in multi-cancer, mutation specific cohorts.

2.2.1. Neratinib-based Combination Treatments

2.2.1.1. Bladder/Urinary Tract Cancer

Newly enrolled patients with *ERBB2* mutant bladder/urinary tract cancer will be treated with the combination of neratinib and paclitaxel. Patients already enrolled and currently on neratinib monotherapy may have paclitaxel added upon progression.

2.2.1.2. Breast Cancer

Patients with *ERBB2* mutant breast cancer will be divided into two different treatment cohorts on the basis of hormone receptor (HR) status: HR negative and HR positive.

- Patients in the HR negative cohort will receive neratinib monotherapy.
- Newly enrolled patients in the HR positive cohort will receive neratinib in combination with fulvestrant irrespective of any previous endocrine therapy, including fulvestrant. Patients with HR positive breast cancers already enrolled and currently on neratinib monotherapy may have fulvestrant added upon progression.

2.2.1.3. Tumor Cohorts Open to Enrollment in Amendment 4

The study will include cohorts with tumors harboring somatic *ERBB* mutations, or *EGFR* gene amplifications as described in Table 1:

Table 1: Tumor Cohorts Open to Enrollment in Amendment 4

Tumor Cohort	Mutation	Assigned Treatment
Bladder/Urinary tract	*ERBB2 Mutant*	Neratinib: 240 mg daily Paclitaxel: 80 mg/m^2 IV on Days 1, 8, and 15 of every 4 week cycle
Biliary tract	*ERBB2 mutant*	Neratinib: 240 mg daily
Breast	*ERBB2 mutant* *HR Negative*	Neratinib: 240 mg daily
	ERBB2 mutant *HR Positive*	Neratinib: 240 mg daily Fulvestrant: 500 mg on Days 1, 15 of the first month, then Day 1 of every 4 week cycle
Endometrial	*ERBB2 mutant*	Neratinib: 240 mg daily
Gastroesophageal[a]	*ERBB2 mutant*	Neratinib: 240 mg daily
Ovarian	*ERBB2 mutant*	Neratinib: 240 mg daily
Solid tumors (NOS)	*ERBB2 mutant*	Neratinib: 240 mg daily

Note: The following cohorts are closed to enrollment in Amendment 4: bladder/urinary tract monotherapy, colorectal monotherapy, breast HR positive monotherapy, lung (NSCLC) monotherapy, primary brain monotherapy, and solid tumors (NOS) ERBB3 mutant monotherapy cohorts.
[a] Gastroesophageal cancers include esophageal, gastro-esophageal and gastric cancers.

If a tumor has more than one qualifying mutation, the patient will be assigned to the appropriate tumor-specified cohort if one exists upon consultation with the Investigator and Sponsor (see Section 1.4 for cohort assignment).

2.3. Investigational Products, Doses, and Administration

2.3.1. 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 5.1).

2.3.2. Fulvestrant

Patients in the HR positive breast cancer cohort (see Table 1) will receive 500 mg total dose of fulvestrant administered as two 5 mL injections, one in each buttock on Days 1, 15, of cycle 1

and then D1 of every 4 week cycle thereafter. 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 5.1).

2.3.3. Paclitaxel

Patients in the bladder/urinary tract cancer cohort treated with combination therapy (see Table 1) will receive 80 mg/m^2 of paclitaxel administered intravenously on Days 1, 8, and 15 of every 4 week cycle.

Dosing should continue until a criterion for treatment withdrawal is met (see Section 5.1).

Refer to local labeling for instructions for appropriate premedication to prevent severe hypersensitivity reactions.

2.3.4. 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.

2.3.4.1. 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 (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 (i.e., diphenoxylate hydrochloride and atropine sulfate [Lomotil], or octreotide [SANDOSTATIN®]) (or equivalent, as approved by the Sponsor) are also recommended for use when appropriate.

2.3.4.1.1. Loperamide

All patients will take loperamide for the first cycle (either 3 or 4 weeks based on cohort cycle length, see Table 2) of neratinib treatment. Patients will take 4 mg TID for the first 14 days with the first dose of loperamide given concomitantly with the first dose of neratinib. After two weeks on study, patients will take 4 mg twice a day (BID) for the remainder of the first cycle of neratinib. Thereafter, loperamide will be administered as needed throughout neratinib treatment. Recommended loperamide dosing is listed below in Table 2.

Table 2: Loperamide Dosing for Neratinib Treatment

Loperamide Dose	Day
4 mg TID with a total daily dose of 12 mg	Days 1-14 (Cycle 1)
4 mg BID with a total daily dose of 8 mg	Days 15-28 (Cycle 1)
Daily dose as needed (not to exceed 16 mg per day)	Days 29+ (Cycle 2 and beyond)

Patients must use a diary to record intake of loperamide during Cycle 1. Loperamide pill counts will be conducted only during Cycle 1 of therapy.

2.3.4.2. 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 2.3.4.3), or drugs with potential for drug-drug interactions (Section 2.3.4.4), 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.
- **Bisphosphonates and receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors (e.g., 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.
- **Secondary prophylactic use of growth factors** (e.g., 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.

2.3.4.2.1. Concomitant Therapy for Bladder/Urinary Tract Cancer Patients

Patients with *ERBB2* mutant bladder/urinary tract cancer currently on neratinib monotherapy may have paclitaxel added upon progression.

2.3.4.2.2. Concomitant Therapy for Breast Cancer Patients

Patients with *ERBB2* mutant HR positive breast cancer currently on neratinib monotherapy may have fulvestrant added upon progression.

2.3.4.2.3. Additional Concomitant Medications for Bladder/Urinary Tract Patients on Paclitaxel Combination Therapy

Bladder/urinary tract patients in the paclitaxel-containing combination cohort should be administered dexamethasone 10 mg IV, completed 30 minutes before each paclitaxel administration (at the Investigator's discretion, dexamethasone may be tapered during the

paclitaxel cycles). Diphenhydramine hydrochloride 50 mg IV and an H_2 blocker IV (ranitidine 50 mg or famotidine 20 mg) should also be given before paclitaxel administration.

2.3.4.3. 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. 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 or prostate cancer on a stable dose of hormonal therapy will be permitted to remain on this regimen through their participation in the study.

2.3.4.4. Potential for Drug-Drug Interactions

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

Patients using drugs known to cause QT/QTc prolongation should be monitored closely with serial electrocardiograms (ECG) at the Investigator's discretion. The study protocol provides a summary of drugs known to have a risk of causing QT/QTc prolongation, potentially causing TdP.

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. The study protocol provides a list of substrates and inhibitors of P-gp.

Patients taking oral coumarin-derivative anticoagulants (e.g., 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), H_2-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 H_2-receptor antagonist such as ranitidine is required, neratinib should be taken 10 hours after the H_2-receptor antagonist dosing and at least 2 hours before the next dose of the H_2-receptor antagonist. If antacids are necessary, the antacid dose and the neratinib dose should be separated by 2 to 4 hours.

3. RULES FOR DOSE MODIFICATIONS

3.1. Investigational Product Dose Adjustment for Toxicity

Investigational product dose adjustment and/or discontinuation should be performed according to Section 5.1, and as described in Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, and Table 12.

Recommended dose reductions for the -1 and -2 dose levels of the investigational product are listed in Table 3.

Table 3: 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
Paclitaxel	80 mg/m^2	70 mg/m^2	60 mg/m^2

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 to be done every 2 cycles, starting from the first dose of IP until the first planned tumor assessment and then after every additional 2 cycles (± 7 days) of treatment regardless of any changes in dose or occurrence of AEs. Missed dose(s) of any IP (i.e., any dose that is not administered within the protocol-defined administration window) 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.

Once the neratinib dose has been reduced for a patient, all subsequent cycles must be administered at that dose, unless further dose reduction is required. Dose re-escalation 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 5.1).

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 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, and Table 12.

Table 4: General Toxicities Requiring Dose Adjustment

NCI CTCAE v.4.0	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
Grade 2 adverse reaction			
1st appearance	Hold **neratinib** until event resolves to Grade ≤1; then resume neratinib at the starting dose level.	No dose adjustment required	No dose adjustment required
2nd appearance	Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg.	No dose adjustment required	No dose adjustment required
3rd appearance	Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg.	No dose adjustment required	No dose adjustment required
4th appearance	Discontinue **neratinib** permanently.	No dose adjustment required	No dose adjustment required
Grade 3 adverse reaction			
1st appearance	Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg.	Hold paclitaxel until recovery to ≤ grade 1 or baseline.	No dose adjustment required
2nd appearance	Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg.	Reduce paclitaxel dose by 1 dose level.	No dose adjustment required
3rd appearance	Discontinue **neratinib** permanently.	If the AE occurs a 3rd time, contact Puma for guidance with patient continuation and appropriate dose adjustments.	No dose adjustment required

Table 4: General Toxicities Requiring Dose Adjustment (Continued)

NCI CTCAE v.4.0	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
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.**	Hold paclitaxel. Contact Puma for guidance for patient continuation on study with appropriate dose adjustments	No dose adjustment required

Based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

Table 5: Gastrointestinal Toxicities Related to Diarrhea Requiring Dose Adjustment

NCI CTCAE V4.0	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
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. Instruct patient to follow dietetic recommendations in the guidelines for management of diarrhea. Fluid intake of ~2L should be maintained to avoid dehydration. Once the event resolved to ≤ Grade 1 or baseline, continue loperamide as per prophylaxis guidelines.	No dose adjustment required.	No dose adjustment required

Table 5: Gastrointestinal Toxicities Related to Diarrhea Requiring Dose Adjustment (Continued)

NCI CTCAE V4.0	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
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** OR **Any Grade 4 diarrhea** [Life-threatening consequences; urgent intervention indicated]	Adjust anti-diarrheal treatment, as per the guidelines for management of diarrhea at the first onset of diarrhea. Hold **neratinib** until recovery to ≤ Grade 1 or baseline. Instruct patient to follow dietetic recommendations of the guidelines for management of diarrhea. Fluid intake of ~2L should be maintained, intravenously if needed. If recovery occurs: ≤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.	For Diarrhea: Grade 3 lasting > 2 days despite treatment with optimal medical therapy, or associated with fever or dehydration: Hold **paclitaxel** until recovery to ≤ Grade 1 or baseline. If recovery occurs ≤1 week of treatment being held, resume same dose of **paclitaxel**. If event recurs, or if recovery >1 week, but not more than 3 weeks of **neratinib** treatment being held continue same dose of **paclitaxel**. If event recurs a 2nd time, reduce dose of **paclitaxel** to the next lower dose level. If event recurs a 3rd time, continue same dose of paclitaxel.	

Table 6: Pulmonary Toxicities Requiring Dose Adjustment

NCI CTCAE V4.0	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
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.	No dose adjustment required	No dose adjustment required
Grade ≥3 Pneumonitis / Interstitial Lung Disease [Severe symptoms; limiting self-care ADL; oxygen indicated]	Discontinue **neratinib** permanently.	No dose adjustment required	No dose adjustment required

Table 7: Liver Toxicity Requiring Dose Adjustment for Fulvestrant Only

Liver Function Toxicity	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
Childs-Turcott-Pugh Class A	NA	NA	Continue 500 mg
Childs-Turcott-Pugh Class B	NA	NA	Reduce dose to 250 mg on same schedule of administration
Childs-Turcott-Pugh Class C	NA	NA	No data in this patient population; consult with medical monitor

Table 8: Liver Toxicity Requiring Dose Adjustment Excluding Fulvestrant

NCI CTCAE V4.0	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
Grade 3 ALT (>5 – 20x ULN) OR Grade 3 bilirubin (>3-10x ULN)	Hold neratinib until recovery to ≤ Grade 1 for patients with ALT ≤ Grade 1 at baseline OR ≤ Grade 2 for patients with Grade 2 ALT at baseline. Evaluate alternative causes. For patients with ALT ≤ Grade 1 at baseline: resume neratinib at the next lower dose level if recovery to ≤Grade 1 occurs within 4 weeks. If Grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue neratinib. For patients with Grade 2 ALT at baseline due to liver metastases: contact the Sponsor for guidance on appropriate dose adjustments.	Hold paclitaxel until recovery to ≤ grade 1 or baseline. Evaluate alternative causes. For patients with ALT ≤ Grade 1 at baseline, resume paclitaxel at the next lower dose level if recovery to baseline occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs despite one dose reduction, permanently discontinue paclitaxel. For patients with ≥ Grade 2 ALT at baseline due to liver metastasis contact Puma for guidance on appropriate dose adjustments.	Refer to Table 7
Grade 4 ALT (>20x ULN) OR Grade 4 Bilirubin (>10x ULN)	Permanently discontinue neratinib. Evaluate alternative causes.	For Grade 4 ALT (>20x ULN): Permanently discontinue paclitaxel. For Grade 4 Bilirubin (>10x ULN): Evaluate alternative causes.	Permanently discontinue Evaluate alternative causes

Table 8: Liver Toxicity Requiring Dose Adjustment Excluding Fulvestrant (Continued)

NCI CTCAE V4.0	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
ALT >3x ULN AND Total bilirubin >2 x ULN AND Alkaline phospatase <2 x ULN (potential Hy's Law indicators of drug-induced liver damage) These events must be reported as SAEs	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. All cases confirmed on repeat testing as meeting the criteria mentioned above, with no other cause for liver function test abnormalities identified at the time should be considered potential Hy's Law cases, irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests. Contact the Sponsor immediately to discuss next steps, including evaluation of alternative causes, and management of IP.	Hold paclitaxel and immediately contact Puma to discuss next steps, including evaluation of alternative causes, and management of paclitaxel.	No dose adjustment required unless Childs-Turcott-Pugh Class B criteria met

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

Table 9: Left Ventricular Ejection Fraction Toxicity Requiring Dose Adjustment

NCI CTCAE V4.0	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
Asymptomatic absolute decline of LVEF ≥15% from baseline OR absolute decline of LVEF ≥10% and below the lower limit of normal of 50%	A) <u>If LVEF below 40%:</u> Hold neratinib and seek cardiology input OR continue neratinib with great caution. Initiate monthly monitoring of LVEF • If while monitoring monthly LVEF remains <40%: reconsider neratinib only if appropriate and after cardiology consult. • If while monitoring monthly LVEF increases to ≥40%: continue neratinib, monitor LVEF every 12 weeks and consider cardiac support with input from cardiologist. B) <u>If LVEF between 40% to 50%</u>: continue neratinib with caution and surveillance Initiate monthly monitoring of LVEF • If while monitoring monthly LVEF falls to <40%: Follow bullet point A instructions described above. • If while monitoring monthly LVEF remains ≥40%: continue neratinib, monitor LVEF every 12 weeks and consider cardiac support with input from cardiology.	No dose adjustment required	No dose adjustment required
Symptomatic cardiac failure	Neratinib should be discontinued.	No dose adjustment required	No dose adjustment required

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

Note that, for AEs other than asymptomatic LVEF decline, if neratinib is held for >4 weeks, the patient should be withdrawn from the treatment stage of the study. In case of asymptomatic LVEF decline, patients may resume neratinib within 1 week after LVEF recovery is documented

as above, even if the timeframe exceeds 4 weeks. If a site does not provide normal ranges for ECHO or MUGA, a lower limit of normal (LLN) of 50% should be used.

Table 10: Infusion Reactions Requiring Dose Adjustment

NCI CTCAE V4.0	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
Dyspnea, clinically significant hypotension	No dose adjustment required	No dose adjustment required unless severe symptoms consistent with severe infusion reactions occur. Then paclitaxel should be permanently discontinued. Neratinib should be continued	No dose adjustment required Neratinib should be continued
Severe infusion reactions	No dose adjustment required	Permanently discontinue	No dose adjustment required

Table 11: Neuropathy Toxicity Requiring Dose Adjustment

NCI CTCAE V4.0	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
Grade 2 neuropathy	No dose adjustment required	Reduce paclitaxel by 1 dose level.	No dose adjustment required
Grade 3 neuropathy	No dose adjustment required	Hold paclitaxel until event resolves or returns to baseline. Decrease paclitaxel dose by 1 dose level.	No dose adjustment required

Table 12: Hematologic Toxicity Requiring Dose Adjustment

NCI CTCAE V4.0	Action with Neratinib	Action with Paclitaxel	Action with Fulvestrant
ANC <1500/mm^3 (1.5 × 10^9/L), or platelet <75,000/mm^3 (75 × 10^9/L) on day of scheduled paclitaxel treatment	No dose adjustment required	Hold paclitaxel until ANC ≥1500/mm^3 (1.5 × 10^9/L), and platelet ≥75,000/mm^3 (75 × 10^9/L). Consider growth factor support with next paclitaxel administration (e.g., G-CSF). If event recurs a 2nd time, hold paclitaxel until ANC ≥1500/mm^3 (1.5 × 10^9/L), and platelet ≥75,000/mm^3 (75 × 10^9/L and reduce paclitaxel by 1 dose level.	No dose adjustment required
Grade 4 neutropenia lasting >7 days, Grade 4 febrile neutropenia, or Grade 3 or 4 infection with Grade 3 or 4 neutropenia (ANC < 1000)	No dose adjustment required	Hold paclitaxel until ANC ≥1500/mm^3 (1.5 × 10^9/L). Consider growth factor support with next paclitaxel administration (e.g., G-CSF). If event recurs a second time, hold paclitaxel until ANC ≥1500/mm^3 (1.5 × 10^9/L) and reduce paclitaxel by 1 dose level.	No dose adjustment required

3.2. Loperamide Dose Adjustments

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 to 2 bowel movements per 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, loperamide should be held until after the first bowel movement and then resumed at a dose reduced to the next-lower dose level.
- If a patient is unable to tolerate once-daily loperamide due to constipation, loperamide should be held and subsequent loperamide dosing discussed with the Medical Monitor.
- Neratinib dosing should continue if loperamide is held.

Recommended dose reductions for constipation due to loperamide are shown in Table 13.

Table 13: Loperamide Dose Reduction Levels for Constipation

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

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

3.2.1. 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, number of stools, and use of loperamide and/or other antidiarrheals. A copy of the Patient Instructions is to be handed to the patient before they leave 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 contains 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 adjusted NCI CTCAE version 4.0 criteria. Also, the daily dose of loperamide (or other antidiarrheals, if applicable) noted on the diary is reviewed and recorded on the CRF.

Loperamide is provided and dispensed directly by the site on or before Cycle 1 Day 1 (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 (Cycle 1)

- 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 first cycle of therapy, regardless of whether or not the patient is experiencing diarrhea.
- 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 antidiarrheal 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 Sponsor's approval).
- The sites must contact the patient by phone 1, 2, and 3 days after the first dose of neratinib in Cycle 1 to inquire about any diarrhea and ensure the patient is compliant with antidiarrheal therapy.
- 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 antidiarrheal medication taken each day for the first cycle of therapy. Patients must record all doses of neratinib for the entire study duration.

For new onset, uncomplicated Grade 1 or Grade 2 diarrhea in Cycle 2 and beyond

Dietetic measures

- Stop all lactose-containing products.
- Drink 8 to 10 large glasses of clear liquids per day.
- Eat frequent small meals.
- Recommend 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 (e.g., fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3 to 4 neutropenia.

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

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

4. MEASUREMENT OF TREATMENT EFFECTS, INCLUDING RESPONSE CRITERIA, DEFINITIONS OF RESPONSE AND SURVIVAL, AND METHODS OF MEASUREMENT

4.1. Efficacy Assessments

Disease evaluation will be performed every 2 cycles by CT (or MRI) and PET/CT. PET/CT is mandatory for all breast cancer patients and optional for RECIST-evaluable patients with other cancers. Radiological response by RECIST v1.1 and metabolic response by PET Response Criteria will be reported and analyzed separately. Complete or partial response (CR or PR) will be confirmed with a repeat scan at the next scheduled interval.

For patients who switch from monotherapy to combination therapy, the disease assessment performed immediately prior to the addition of the combination therapy will constitute the new baseline of measurable disease for the combination. This should be used as the comparator for future response assessments performed at 2-cycle intervals.

4.2. Safety Assessments

Patients receiving at least one dose of the IPs are evaluable for safety.

Safety is assessed based on medical history, vital sign measurements, physical examination findings, electrocardiogram (ECG) results, cohort-specific multigated acquisition scan (MUGA) or echocardiogram (ECHO), laboratory assessments, and AEs. Adverse events are graded according to the National Cancer Institute Common Terminology Criteria (NCI CTC) version 4.0. Adverse events and serious adverse events (SAEs) are reported until 28 days after the last dose of IP(s) and are followed until resolution or the condition stabilizes.

It should be promptly reported if an Investigator is made aware of any SAEs occurring any time after the reporting period that may be causally related to neratinib administration.

The Investigator’s assessment of causality must be provided for all AEs (serious and nonserious); the Investigator must report this assessment in accordance with 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 is handled as “related to investigational product” for reporting purposes, as defined by the Sponsor. If the Investigator's causality assessment is “unknown but not related to investigational product,” this should be clearly documented.

For all AEs, the Investigator should obtain sufficient information to determine the causality of the AE. The relationship of the AE to the study treatment (IP or other concomitant medications) is assessed using these definitions:

- 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.

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

4.3. Other Assessments

4.3.1. Tumor Specimens

All efforts will be made to collect tumor specimens for retrospective centralized confirmation of somatic mutations in the ERBB gene family (EGFR, ERBB2, ERBB3). This tumor sample should preferably be from the specimens used to detect the initial mutation or gene aberration prior to study enrollment. Unless a fresh biopsy presents a safety issue for breast cancer patients, a mandatory pretreatment fresh core biopsy will be collected and subject to central confirmation of ERBB2 mutations.

4.3.2. Cell-free DNA Analysis

Whole blood for germline DNA analysis will be collected once at screening. Cell free DNA (cfDNA) will be obtained from plasma samples collected at screening, every 2 cycles and at time of treatment discontinuation; cfDNA will be subject to molecular profiling to identify ERBB2 mutations and other gene aberrations related to treatment response and resistance.

4.3.3. Quality of Life Assessments

Patient reported outcomes using the EQ-5D-5L (EuroQol Group Association**)** assessment will be performed at 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.

4.4. 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 amount 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 (SOPs), 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 5.2).

5. REASONS FOR EARLY CESSATION OF STUDY THERAPY

5.1. Investigational Product Discontinuation

Patients **must** be discontinued from the **IPs** (but may remain in the study for long-term follow-up, if appropriate), under the following circumstances listed in this section and in Section 3.1, unless otherwise agreed with the Medical Monitor:

- If the patient requires more than 2 dose reductions of IP (Section 3.1).
- If the IP is withheld due to a neratinib-related AE for >28 days; patients who are clinically benefiting from therapy with neratinib may resume therapy after 28 days if the Sponsor approves in advance.
- Disease progression: patients who, in the opinion of the Investigator, continue to benefit from neratinib despite disease progression may continue to receive neratinib if the Sponsor approves in advance.
- Pregnancy
- Investigator request
- Patient request (i.e., 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 and PFS if the event leading to treatment discontinuation occurs prior to the first postbaseline 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)

5.2. 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)
- Individual patient dosing noncompliance.

- Lost to follow-up (defined as receiving no response after 3 attempts at contact by phone followed by 1 attempt by sending a certified letter).
- If the entire study is terminated prematurely

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

5.3. 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. Patients who discontinue due to an AE 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 CRF and the Investigator's copy of the ICF, which the patient will countersign and date.

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 5.1), or at the Investigator's discretion. Upon confirmed disease progression, or IP discontinuation 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.

6. OBJECTIVES AND ENTIRE STATISTICAL SECTION, INCLUDING ENDPOINTS

6.1. Primary Objectives

To determine the objective response rate at 8 weeks (ORR_8) for all cohorts.

6.2. Secondary Objectives

The secondary objectives of this study are:

- To determine the confirmed objective response rate (ORR) according to RECIST v1.1 or other defined response criteria with neratinib monotherapy and combination therapy.
- To determine the clinical benefit rate (CBR) of neratinib monotherapy and combination therapy.
- To determine PFS.
- To determine change in tumor growth rate for patients with primary brain tumors.
- To determine the duration of response (DOR) of neratinib monotherapy and combination therapy, defined as the time from which measurement criteria are met for overall response of CR and PR until the first date of documented disease progression.
- To determine overall survival (OS).
- To determine the role of dual modality PET/CT scans in measuring metabolic response to neratinib monotherapy and combination therapy.
- To assess the safety profile and tolerability of neratinib monotherapy and combination therapy.
- To assess Patient Reported Outcomes using the EuroQol EQ-5D-5L instrument.

6.3. Exploratory Objectives

- To collect and retrospectively evaluate human *ERBB* mutations (*EGFR*, *ERBB2*, *ERBB3*) or *EGFR* amplification status in pretreatment archival tissue and in pretreatment fresh biopsies at a central laboratory.
- To collect and retrospectively evaluate the *ERBB2* mutations using next-generation (NGS) or whole-exome (WES) sequencing in fresh core pretreatment biopsies in patients enrolled in the breast cancer cohorts.
- To explore genetic modifiers of sensitivity to neratinib in solid tumors with mutations in *ERBB* genes including *EGFR*, *ERBB2*, and *ERBB3* using molecular profiling techniques in pretreatment archival, 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, or upon disease progression to identify *ERBB* 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 (all cohorts optional except the primary brain tumor cohort where a tissue biopsy is required at time of surgery and for all breast cancer patients where a fresh tumor biopsy is mandatory) during time of treatment and/or at the time of treatment discontinuation or disease progression.
- To determine concentrations of neratinib in brain tumors tissues and corresponding blood-derived samples.

6.4. Statistical Methods

The statistical considerations summarized in this section outline the plan for data analysis of this study.

6.4.1. 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 analysis population is defined as all patients who received at least 1 dose of neratinib monotherapy or combination therapy. This population will be used for all efficacy and safety analyses, if not otherwise specified.

The efficacy evaluable population for the Simon 2-stage is defined as all patients who are enrolled into the study, have completed at least 1 week of treatment with neratinib monotherapy or combination therapy, and have at least 1 post-baseline tumor assessment completed.

6.4.2. 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.

For patients who switch from monotherapy to combination therapy, the disease assessment performed immediately prior to the addition of the combination therapy will constitute the new baseline of measurable disease for the combination. This should be used as the comparator for future response assessments performed at 2-cycle intervals. The efficacy and safety on combination therapy will be summarized separately starting from the start time of combination therapy.

6.4.2.1. Primary Endpoint and Sample Size

The primary goal of this study in all cohorts is to determine the objective response rate following 2 cycles of treatment (ORR_8) who have solid tumors that have human somatic mutations in the *ERBB* gene family (*EGFR*, *ERBB2*, and/or *ERBB3*) or *EGFR* gene amplification per RECIST version 1.1 or other defined response criteria. The efficacy response is assumed binary, i.e., a patient is a responder (achieving CR or PR) versus non-responder based upon criteria outlined in Section 4.1.

The sample size required for each cohort depends on objective response rates (ORR_8) at 8 weeks that are defined as clinically inadequate and promising for further investigation. A clinically inadequate ORR_8 will be defined as 10%, which is derived from historical control estimates. A promising ORR_8 will be defined as 30%. The definition for a promising ORR_8 is lower than ORRs previously observed in other trials (Zhou et al, 2011; Chapman et al, 2011), 50% to 60% response, which accrued patients with one or two activating mutations that were specifically targeted for the therapy being studied. In contrast, this study will enroll patients with tumors that have activating somatic *ERBB* mutations (*EGFR*, *ERBB2*, and/or *ERBB3*) or *EGFR* gene amplification, which may result in a lower ORR_8 than observed with *ERBB2*-positive breast cancer.

A Simon 2-stage optimal design (Simon, 1989) will be used to determine whether neratinib monotherapy or combination therapy has sufficient activity to warrant further development in all the cohorts excluding bladder/urinary tract monotherapy, *ERBB2*, and *ERBB3* NOS cohorts. 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%), a true ORR_8 of 10% or less will be considered unacceptable (null hypothesis) whereas a true ORR_8 of minimally 30% (alternative hypothesis) will merit further study. In the first stage, enrollment will continue until 7 patients per the Simon 2-stage design have completed 2 cycles of neratinib monotherapy or combination therapy and the appropriate efficacy assessment has been completed. If no responses are observed, enrollment in the second stage for the cohort may be discontinued at the Data Review Committee's (DRC) discretion. Otherwise, upon the DRC's recommendation, the second stage will open and 11 additional response evaluable patients will be assessed 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 each cohort. At the end of the trial, a 2-sided 80% confidence interval for ORR_8, consistent with the study design, will be determined for each cohort separately using the method of Koyama and Chen (2008).

Enrollment to *ERBB2* and *ERBB3* mutant solid tumors NOS and to *EGFR* mutant/amplified primary brain tumor cohorts may enroll approximately 30 patients or more per cohort. Enrollment to the bladder/urinary tract monotherapy cohort may enroll up to 20 patients. A sample size of 30 patients will provide an 80% confidence interval on the response rate with at most 13% as the half width. For example, if the response rate is 50%, the confidence interval will be 50% ±13. If the solid tumor cohorts do not enroll a sufficient number of patients to perform the requisite 2-stage analysis, descriptive statistics, without taking into account of the 2-stage design, will be computed.

A new tumor-specific *EGFR* mutation cohort or *EGFR* amplification cohort may be opened separately from within any *ERBB2* or *ERBB3* mutant NOS cohort and follow the Simon 2-stage criteria.

Once the Simon 2-stage criteria are met for the *ERBB2* mutant HR positive breast combination cohort, enrollment into this cohort may continue until approximately 50 evaluable patients have been enrolled. The *ERBB2* mutant HR negative breast cohort will follow Simon 2-stage criteria. A new cohort may also be opened separately at any time per Sponsor discretion and follow the Simon 2-stage criteria. Cohorts may close prior to planned enrollment.

A Data Review Committee (DRC) will be established to regularly review accumulating safety data (by individual patient and in aggregate) and efficacy data at the end of Stage 1 for each relevant cohort. The DRC consists of at least 2 Investigators from at least 2 investigational sites that are external to the study Sponsor and functional representatives (medical, safety, and biostatistics at a minimum) from the Sponsor. The decision to proceed from Stage 1 to Stage 2 for each cohort will be made by the DRC.

Table 14: Sample Size, Non-2-Stage, and Simon 2-Stage Rules

Cancer Cohort		
Simon 2-Stage Cohorts	**Stage 1**	**Stage 2**
1. *ERBB2* mutation		
Biliary (Monotherapy Cohort)	≥1/7	≥4/18
Bladder/Urinary Tract (Combination Treatment Cohort)	≥1/7	≥4/18
Breast Cancer HR - (Monotherapy Cohort)	≥1/7	≥4/18
Breast Cancer HR + (Combination Treatment Cohort)	≥1/7	≥4/18
Colorectal (Monotherapy Cohort)	≥1/7	≥4/18
Endometrial (Monotherapy Cohort)	≥1/7	≥4/18
Gastroesophageal (Monotherapy Cohort)	≥1/7	≥4/18
Lung (Monotherapy Cohort)	≥1/7	≥4/18
Ovarian (Monotherapy Cohort)	≥1/7	≥4/18
Non-2-Stage Cohorts		
1. *ERBB2* mutation		
Bladder/Urinary Tract (Monotherapy Cohort)	Non-2-Stage: n=20 patients or more	
Solid tumors NOS	Non-2-Stage: n=30 subjects or more	
2. *EGFR* mutation and/or *EGFR* amplification-positive		
Primary brain tumors (glioblastoma multiforme [GBM] Grade III, glioma, gliosarcoma [Louis et al, 2007]) with an *EGFR*-mutation or amplification	Non-2-Stage: n=30 patients or more	
3. *ERBB3* mutation		
Solid tumors NOS	Non-2-Stage: n=30 patients or more	

Note: If a tumor harbors more than one qualifying mutation, then the patient will be assigned to the appropriate, tumor-specified cohort if one exists.
Abbreviations: EGFR = human epidermal growth factor receptor, HR = hormone receptor, NOS = not otherwise specified.

6.4.2.2. Secondary Endpoints

The confirmed ORR will be estimated and its associated 2-sided 80% and 95% Clopper-Pearson confidence intervals will be determined.

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 80% and 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 at the initiation of new anticancer therapy. Median PFS will be estimated via Kaplan-Meier with its associated 2-sided 80% and 95% confidence intervals.

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 80% and 95% confidence intervals.

In addition, OS for each cohort will be estimated using Kaplan-Meier method.

The role of dual modality PET/CT scans will be evaluated in measuring response to neratinib monotherapy and combination therapy.

The safety profile and tolerability of neratinib monotherapy and combination therapy will be assessed in patients treated in this study.

Patient reported outcomes will be evaluated using the EuroQol EQ-5D-5L questionnaire. The assessments will be summarized and plotted over time. Changes from baseline will be provided with both point estimates and confidence intervals.

6.4.2.3. 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 the primary brain tumor cohort where a tissue biopsy is required at the time of surgery in eligible patients and for all breast cancer 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.

The concentration of neratinib in collected brain tumor tissues and corresponding blood-derived samples will be assessed.

No formal statistical analysis is planned for these exploratory objectives.

6.4.2.4. 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. Adverse events and serious AEs will be coded using 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.

6.4.2.5. 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.

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