An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients With HER2 Amplified Breast Cancer Treated With Neratinib

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STATISTICAL ANALYSIS PLAN

Protocol Title:	An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients With HER2 Amplified Breast Cancer Treated With Neratinib
Study Protocol No.	PUMA-NER-6203
Disease Condition	HER2 Amplified (HER2+) Breast Cancer
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LIST OF ABBREVIATIONS

Abbreviation	Term/Definition
AE	adverse event
AESI	adverse events of special interest
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
HER	human epidermal growth factor receptor
HER2	human epidermal growth factor receptor 2 (neu [N ethyl nitrosourea stimulated] gene product); also known as c erB2, ERBB2, or p185
IP	Investigational Product
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mBC	metastatic breast cancer
mg	Milligrams
MUGA	multiple-gated accession scan
NCI	National Cancer Institute
PT	preferred term
QTc	QT interval, corrected for heart rate
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event

1. PURPOSE OF ANALYSIS

The statistical analysis plan (SAP) outlines details of the statistical methods and analyses of the protocol **"An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients With HER2 Amplified Breast Cancer Treated With Neratinib" (**PUMA-NER-6203), dated 04 September 2019.

The purpose of the SAP is to pre-specify analyses that are consistent with the protocol objectives to ensure appropriate interpretation of the data. It supplements the statistical section specified in the protocol with additional details and clarity related to the statistical analyses. The SAP must be finalized prior to database lock according to standard operating procedures. Deviations from this plan will be documented and described in the CSR.

2. PROTOCOL SUMMARY

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to characterize and understand colon pathogenesis related to neratinib-induced diarrhea through biopsies and images obtained by colonoscopy study

This objective will not be addressed by PUMA in this SAP.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To characterize the incidence and severity of diarrhea during the first 28-day cycle.
- To analyze changes in serological and fecal inflammatory markers from baseline to second colonoscopy.

2.2 Study Endpoints

2.2.1 Primary Endpoint

The primary endpoint is change from baseline in pathological findings in colon biopsies after the first 28 days of neratinib monotherapy.

2.2.2 Secondary Endpoints

The secondary endpoint will be the incidence and severity of diarrhea during the first 28-day cycle of neratinib monotherapy.

2.3 Overall Study Design and Plan

2.3.1 Study Design

This is an open-label, phase 2 study that will investigate colon pathology in patients with HER2-positive breast cancer treated with neratinib as monotherapy.

All patients will receive neratinib for the first 28 days as a single daily dose of 240mg.

Following the second study colonoscopy procedure:

- For patients being treated for stage 1 to 3c breast cancer in the extended adjuvant setting, neratinib will continue to be administered at a single daily dose of 240mg until completion of one year of therapy from start of treatment , or until disease

recurrence (as determined by the Investigator), death, unacceptable toxicity, or other specified withdrawal criterion.

- For patients being treated for metastatic breast cancer (mBC), capecitabine will be introduced after the second study colonoscopy procedure at a dose of 750mg/m^2 twice daily for 14 days of each 21 day treatment cycle, with neratinib administered continuously throughout at 240mg daily, until disease progression, death, unacceptable toxicity, or other specified withdrawal criterion.

All patients will receive loperamide diarrhea prophylaxis daily for one (1) 28-day cycle and then as needed.

Following a 28-day screening period, eligible patients will be enrolled. Baseline assessments will be performed prior to Cycle 1/Day 1 dosing. Patients will then participate in the active treatment phase, consisting of, in both groups, a single 28-day cycle of neratinib monotherapy. Neratinib and loperamide will be administered orally by patients. The morning dose of neratinib will be held on the day of the second study colonoscopy procedure.

Colonoscopy will be performed after eligibility has been confirmed, but prior to administration of the first dose of neratinib on Day 1 of Cycle 1, and at Day 30 (± 3 days). Thereafter, extended adjuvant patients with stage 1 to 3c breast cancer will continue to receive neratinib monotherapy for 1 year or until progression of disease, death, or intolerance to study prescribed therapy. Patients with mBC will continue to receive neratinib in 21-day cycles, beginning in Cycle 2, after completion of the second study colonoscopy procedure, in combination with capecitabine administered on Day 1-14 of each cycle, until progression of disease, death, or intolerance to study prescribed therapy.

NOTE; patients with mBC cannot be exposed to capecitabine until after completion of the second study colonoscopy procedure.

In extended adjuvant patients with stage 1 to 3c breast cancer, patients will return to the clinic approximately every 3 months for safety assessments. End of Treatment (EOT) visit is planned on upon completion of 1 year of treatment, followed by Safety Follow-up Visit 28 days after the last dose of neratinib.

In patients with mBC, clinic visits during the active treatment phase are planned on Day 1 of Cycle 1, Cycle 2, and each subsequent cycle. Treatment discontinuation visit is planned 0-3 days after the last dose, followed by a Safety Follow-up Visit 28 days after the last dose of neratinib.

The study will end when all patients have been followed-up for 28 days after the last dose of neratinib.

Approximately 3-5 patients will be enrolled at approximately 2 centers.

The approximate duration of the study is 1.5 years.

Patients with stage 1 to 3c disease receiving extended adjuvant therapy are anticipated to participate in the study for approximately 1 year. This includes 1 month for screening, approximately 12 months for the active treatment phase until progression of disease or intolerance to study prescribed therapy, and safety follow-up visit 28 days after the last dose of neratinib.

Patients with mBC are anticipated to participate in the study for an average of 12 months. This includes approximately 1 month for screening, an estimated average of 9.5 months for the active treatment phase, and an estimated average of 1 month for initial Safety Follow-up. Patients who permanently discontinue treatment due to unacceptable toxicity will be followed-up for 28 days after the last dose of neratinib to collect any adverse events (AEs) (Section 9.4).

The primary analysis will be conducted after all patients have completed two sets of colon biopsies. The final analysis will be conducted when all patients with stage 1 to 3c breast cancer have completed 1 year of study treatment or have met other specified withdrawal criteria and patients with mBC have discontinued therapy or have met other specified withdrawal criteria.

The study will end when all patients have been followed up for 28 days after the last dose of neratinib.

In the event that end of treatment (EOT) is declared earlier by the Sponsor, patients will be offered the opportunity to complete treatment through a treatment extension study.

2.3.2 Neratinib Adjustments

Neratinib may be dose-adjusted/reduced due to neratinib-related toxicity. The prescribed dose levels can be 240mg, 200mg, 160mg, 120mg, with the latter three doses representing the reduction levels. If doses of neratinib are held, study procedures for that cycle will proceed on schedule as planned, without any delay. Missed dose(s) of neratinib (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 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 must discontinue the investigational product if a criterion for withdrawal is met.

Reintroduction of the discontinued investigational product at a later time during the active treatment phase is not permitted.

2.3.3 Loperamide

- The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.
- During weeks 1-2 (day 1 – 14) of Cycle 1 loperamide 4 mg will be self-administered administered three time daily.
- During weeks 3-4 (days 15 – 28) of Cycle 1 loperamide 4 mg will be self-administered twice daily
- After the first 28 days, loperamide will be self-administered as needed (PRN) (not to exceed 16 mg per day).

2.3.4 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).

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

Loperamide dose reduction levels for constipation are:

- Dose Level 0 (4mg TID or 6 tablets/capsules a day)
- Dose Level -1 (4 mg BID or 4 tablets/capsules a day)
- Dose Level -2 (2mg TID or 3 tablets/capsules a day)
- Dose Level -3 (2 mg BID or 2 tablets/capsules a day)
- Dose Level -4 (2 mg once a day or 1 tablet/capsule a day)

If a patient experiences an AE leading to dose interruption of neratinib for reasons other than diarrhea, consider holding loperamide until neratinib treatment is resumed.

2.3.5 Capecitabine

Patients with mBC will receive capecitabine, beginning in Cycle 2 of treatment (i.e., following completion of the second study colonoscopy procedure and biopsy).

Capecitabine is available at 150 mg and 500 mg film-coated tablets.

Capecitabine (total dose of 1500 mg/m^2 daily, administered as 750 mg/m^2 in approximately evenly divided doses) will be self-administered orally by patients starting with Cycle 2/Day 1 (i.e. following completion of the second study colonoscopy procedure and biopsy). Doses are to be taken daily on Days 1 to 14 of each 21-day cycle. Capecitabine should be taken with water within 30 minutes after a meal.

During treatment with neratinib plus capecitabine, patients should be monitored for conditions that may require dose to be held or discontinued. Careful attention should be paid to the onset of diarrhea or hand-foot syndrome in particular, and early dose adjustment or prophylactic therapy should be implemented.

Daily dose of neratinib plus capecitabine should continue until a criterion for treatment withdrawal or study withdrawal is met.

2.3.6 Capecitabine Dose Adjustment

Recommended dose reductions for capecitabine-related toxicity in combination with neratinib are listed below:

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

2.4 Study Population

Approximately 3-5 patients will be enrolled.

3. DEFINITIONS

Baseline

The baseline value for a parameter of interest is the last measurement obtained prior to or on the date of the first dose of neratinib.

Cycle

The first cycle is 28 days for all subjects, all of whom receive neratinib and loperamide prophylaxis. After the first 28-day cycle, stage 1 to 3c breast cancer patients receiving extended adjuvant treatment return to clinic every 3 months. Metastatic breast cancer patients return to clinic at scheduled 21-day cycles, during with time they receive both neratinib and capecitabine.

Study Day 1

Study Day 1 is the date the first dose of neratinib is taken.

Treatment duration

Treatment duration in days = last dose date - first dose date + 1

Actual Dose Intensity

The actual dose intensity is defined as the cumulative actual dose divided by treatment duration.

Relative Actual Dose Intensity

The relative actual dose intensity is defined as the actual dose intensity divided by the planned dose intensity.

Prescribed Dose Intensity

The prescribed dose intensity is defined as the cumulative prescribed dose divided by treatment duration.

Treatment-Emergent Adverse Event (TEAE)

A TEAE is defined as an AE that occurs or worsens on or after the first administration of neratinib and up to 28 days after the second colonoscopy in patients with stage 1 to 3c breast cancer, and following completion of Cycle 2 in mBC patients.

Investigational Product (IP)

Investigational product (IP) is used to reference neratinib and capecitabine.

4. DATA SCREENING, ACCEPTANCE AND PROGRAMMING

4.1 General Principles

Clinical data are entered into the Medrio database. Data cleaning and query resolution are performed according to the study specific data management plan. Prior to any formal analysis, a data cut-off date will be established by the clinical study team to ensure appropriate cleaning and query resolution of data up to the data cut-off date. Data extracts in SAS formats will be taken from a snapshot of the live database or a locked database will be used for the analyses.

The clinical study team will identify the criteria for important protocol deviations. Important protocol deviations will be summarized and listed in the clinical study report.

4.2 Handling of Missing and Incomplete Data

Missing and incomplete data will be identified for investigation, and possible resolution, as part of the data cleaning. At the analysis time, missing data will be treated as missing, unless otherwise specified. Missing and incomplete dates for adverse events, concomitant medications, and historical data may be imputed for certain analyses.

Partial dates will be defined as dates that are missing certain elements of the date field. This may include missing information for the month, day or year, or two of these elements, but not all three. If either month or year is missing or the date is completely missing then no data imputation will be implemented.

AEs with completely missing start dates will be considered as treatment-emergent adverse events unless there is clear evidence that the AEs start prior to the first dose.

4.3 Testing/Validation Plan

Statistical programming will be performed using SAS software, version 9.4 or higher, on a Windows Server OS. All SAS programs will be documented, QC'ed, written in accordance with department SOPs.

Analyses performed by statistical software other than SAS are permitted if the analyses cannot be readily performed in SAS. All statistical programming must follow commonly accepted practice including adequate comments within the program, code review, logic review, and check of program log. Key analysis results may require additional validation including but not limited to independent programming.

5. ANALYSIS POPULATIONS

5.1 Safety Population

The safety population is defined as all enrolled patients who have received at least one dose of neratinib.

6. ANALYSIS METHODS

A minimum of 2 analyses will be conducted: primary and final. The primary analysis will occur after all patients have completed the second study colonoscopy. The final analysis will occur after all patients have either discontinued or completed study treatment. Unless otherwise indicated, all data will be presented at both analyses and only in the form of listings.

In the case of data summaries, for continuous endpoints, the sample size (n), mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3) , minimum, and maximum will be provided. For discrete data, the frequency and percent distributions will be provided.

6.1 Disposition of Patients

Reasons for treatment discontinuation and study discontinuation will be listed.

6.2 Deviations

A listing will be provided for protocol deviations.

6.3 Demographic and Baseline Characteristics

A listing will be provided for demographics, which will include age at study enrollment, sex, ethnicity, race, menopausal status, height (cm), weight (kg), and BMI (kg/m^2).

6.4 Medical History

Medical history will be listed by system organ class and preferred terms.

6.5 Cancer History

6.5.1 Summary of Cancer History

A listing will be provided. The listing will include ECOG performance status and disease setting.

6.5.2 Prior Anti-cancer Medications

A listing will be provided for prior anti-cancer medications. The listing will include status (yes/no) of prior anti-cancer medication, indication (neoadjuvant, adjuvant, metastatic/locally advanced).

6.6 Serological and Stool Parameters

Listings will be provided for the following parameters: serological inflammatory markers and stool inflammatory markers, along with applicable data elements from each form.

6.7 Study Medications

6.7.1 Study Medication (Neratinib)

Exposure to neratinib during the study will be listed. Variables will include treatment duration in months, cumulative actual dose (mg), actual dose intensity (mg/day), relative actual dose intensity, cumulative prescribed dose, prescribed dose intensity, and compliance. The compliance for neratinib is calculated by using actual dose intensity divided by the prescribed dose intensity.

Indicator for dose reduction (yes/no), dose reduction due to AE (yes/no), and the lowest dose reduction level, will be included in the listing. In addition, indicator for the dose withheld due to AE (yes/no) will be included.

6.7.2 Study Medication (Capecitabine)

A listing will be provided for capecitabine exposure, which will include treatment duration (months), cumulative actual dose (mg/m^2), actual dose intensity (mg/m^2/day), relative actual dose intensity (%).

Indicator for dose reduction (yes/no) and dose reduction due to AE (yes/no) and the lowest dose reduction level will be included in the listing. In addition, indicator for dose withheld due to AE (yes/no) will be included.

6.8 Concomitant Medications and Therapy

Concomitant medications will be listed by Anatomical Therapeutic Chemical (ATC) category and preferred term.

6.8.1 Loperamide During the First Cycle

Exposure to loperamide during the first cycle (28 days) will be listed by treatment duration (days), cumulative actual dose (mg), actual dose intensity (mg/day) and relative actual dose intensity. In addition, the initial loading dose will also be provided.

The highest daily dose, lowest daily dose, dose reduction due to AE (yes/no), dose increase due to AE (yes/no), and dose hold due to AE (yes/no).

For loperamide, for the first 14 days, the planned dose intensity is 12mg/day; for days 15 through 28, the planned dose intensity is 8 mg/day. The planned dose intensity for loperamide for the first cycle is (12mgx14days + 8mgx14days)/28 = 10mg/day.

6.8.2 Anti-diarrheal Medication During the First Cycle

All anti-diarrhea medication (including loperamide and any other concomitant medication for diarrhea) during the first cycle, will be listed to include the anti-diarrhea medication name and anti-diarrheal medication use duration.

6.8.3 Concomitant Therapy

Concomitant therapy will be listed.

6.9 Adverse Events (AEs)

AEs are graded by the investigators according to the NCI CTCAE v.4.0. AEs will be coded using MedDRA. Summaries will focus on treatment-emergent adverse events (TEAEs).

6.9.1 Treatment-emergent Diarrhea

Additional summaries will be provided for incidence of diarrhea by worst grade, and incidences of serious, treatment-related, and serious treatment related diarrhea, as well as the incidences of the action taken categories as a result of the diarrhea event, and the outcome of the last episode of diarrhea. The time to onset of first treatment emergent diarrhea, duration of treatment emergent diarrhea per episode and per patient and will be summarized. Same summaries will be repeated for grade 2 or higher diarrhea and grade 3 or higher diarrhea. The incidence of dose interruption due to diarrhea, dose reduction due to diarrhea and the number of dose interruptions and time to the first dose reduction and interruption will also be summarized.

6.9.2 Treatment-Emergent Adverse Events (TEAEs)

A high-level summary of TEAE will be provided and select summaries of TEAE subgroups (indicated in parentheses).

TEAEs will also be presented in incidence tables by system organ class (SOC), preferred term (PT), and grade for the following:

- Any TEAE (summary)
- Treatment-related TEAE
- Serious TEAE
- Serious treatment-related TEAE
- Grade 3 or 4 TEAE (summary)
- Fatal TEAE (summary)
- TEAE leading to dose reduction
- TEAE leading to dose interruption
- TEAE leading to treatment discontinuation

Incidence tables of TEAEs in descending order of frequency by PT will be presented for any TEAE, Grade 3 or 4 TEAE, and fatal TEAE.

Listings will be provided for SAEs, TEAEs, and TEAEs leading to study drug discontinuation.

6.9.3 Adverse Events of Special Interest (AESI)

The AESI for neratinib will be based on SMQ or the complete list of the Sponsor-defined group of PTs. Tables will be provided with a summary of the incidence of all AESI by PT and Grade.

6.9.4 Death

If applicable, deaths will be listed with the following variables: indicator of death (yes/no), on-study deaths (within 28 days after last dose of neratinib) (yes/no), and cause of death.

6.10 Clinical Laboratory Parameters

Laboratory data will be listed by visit/collection timepoint.

Listings of laboratory values for blood chemistry parameters and hematology parameters will be provided.

In addition, abnormalities in liver function tests will be listed.

6.11 Vital Signs

Vital sign measures (systolic and diastolic blood pressure, pulse, respiratory rate, oral temperature and weight) will be listed.

6.12 ECG Abnormality

Electrocardiograms (ECGs) are measured after resting in a supine position for 5 minutes and include Heart rate, Rhythm pattern, RR interval PR interval, QRS interval, QT interval, QT_c interval-Bazett's, QTc interval-Fridericia's, QTc interval-Other. Overall evaluation is also indicated.

A listing of ECGs will be provided.

6.13 Left Ventricular Ejection Fraction (LVEF)

LVEF data will be listed.

6.14 Disease Recurrence

Disease recurrence data will be listed.

7. INTERIM ANALYSES

Not applicable

8. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Not applicable

9. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

9.1 TABLES

Tables
Summary of treatment-emergent diarrhea characteristics
TEAE (high-level summary)
TEAE by SOC, PT, and Grade
Grade 3 or 4 TEAE by SOC, PT, and Grade
Fatal TEAE by SOC, PT, and Grade
TEAE in descending order of incidence by PT
Grade 3 or 4 TEAE in descending order of incidence by PT
Fatal TEAE in descending order of incidence by PT
AESI by event category, PT, and Grade
Incidence of liver function test abnormality

9.2 LISTINGS

Listings
Listing of disposition
Listing of deviations

Listing of demographics
Listing of cancer history
Listing of prior anti-cancer medications
Listing of serological parameters
Listing of stool parameters
Listing of neratinib exposure
Listing of capecitabine exposure
Listing of loperamide exposure
Listing of concomitant therapy
Listing of SAEs
Listing of TEAEs
Listing of TEAEs leading to IP discontinuation
Listing of deaths
Listing of laboratory values, blood chemistry
Listing of laboratory values, hematology
Listing of liver function test values
Listing of ECGs
Listing of Vital Signs
Listing of LVEF
Listing of disease recurrence

10. REFERENCES

Study Protocol Number PUMA-NER-6203: An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients With HER2 Amplified Breast Cancer Treated With Neratinib. PUMA Biotechnology, 04 September 2019.

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