Official Title: **A Phase 2 Study of Poziotinib in Patients with HER2-Positive Metastatic Breast Cancer (MBC) Who Have Received Prior HER2 Regimens for MBC**

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CONFIDENTIAL
STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2 Study of Poziotinib in Patients with HER2-Positive Metastatic Breast Cancer (MBC) Who Have Received Prior HER2 Regimens for MBC
Study Number:	SPI-POZ-201
Study Phase:	Phase 2
Study Drug:	Poziotinib
IND Number:	127,487
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Summary of Changes for Version 2

The purpose of Version 2 is to accommodate changes in Protocol Amendment 1 and Amendment 2, and to provide more details. Important changes are summarized below.

Overall:

- Two lower dose cohorts were added due to the original dose level was not well tolerated.
- The study changed from test of hypotheses study to proof-of-concept study.
- New sections are added to provide details for tumor assessments and response evaluation.

Section 2: Objectives modified to match protocol change.

Section 3:

- Additional cohorts added to match protocol change.
- Modifications made for sample size considerations to match protocol change.
- New section added for “Tumor Assessments” to provide details.

Section 4: Modified to match protocol.

Section 5.1: Modified for clarification.

Section 5.2:

- New section added for “Protocol Deviation”.
- “Drug Exposure” moved to Section 5.4.

Section 5.3:

- New section added for “Best Overall Response” to provide details.
- Wording modifications to accommodate new sections.
- Remove “Overall Survival” to match protocol change.
- Add subgroup analysis.

Section 5.4:

- “Drug Exposure” moved from Section 5.2 and modified.
- Wording modifications for clarity.

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1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within Protocol Amendment 2 for Study SPI-POZ-201, dated 14 Jul 2017. The scope of this plan includes all efficacy and safety analyses of poziotinib in patients with HER2-positive Metastatic Breast Cancer (MBC) who have received prior HER2 regimens for MBC. The PK analysis will be covered in a separate analysis plan.

2 OBJECTIVES

2.1 Primary Objective

- To establish the dosing schedule for poziotinib to be used in the clinical development program
- To evaluate the Objective Response Rate (ORR) of poziotinib in patients with human epidermal growth factor receptor 2 (HER2)-positive MBC

2.2 Secondary Objectives

- To assess the safety and tolerability of poziotinib in patients with HER2-positive MBC
- To evaluate the pharmacokinetics of poziotinib in patients with HER2-positive MBC
- To evaluate other efficacy variables of poziotinib in patients with HER2-positive MBC, including the following:
  - Progression Free Survival (PFS)
  - Disease Control Rate (DCR)
  - Time to Progression (TTP)

3 STUDY OVERVIEW

This is a Phase 2, open-label, multicenter study to establish the dose regimen and evaluate the preliminary efficacy and the safety / tolerability of poziotinib in approximately 75 patients with HER2-positive MBC who have received at least 2 prior HER2-directed treatment regimens including trastuzumab and T-DM1.

The Screening period (Day -30 to Day -1) lasts up to 30 days prior to Cycle 1, Day 1. Patients must meet all Inclusion/Exclusion Criteria to participate in the study. Eligible patients will provide written Informed Consent prior to undergoing any study procedures.

Each treatment cycle will be 21 days in duration. The original protocol contained only **Cohort 1**. In Amendment 1, patient enrollment in **Cohort 1** was complete, and new patients began enrollment into **Cohort 2**. **Cohort 2** was continued after two Safety Data Reviews and no patient was enrolled into additional cohorts.

Cohort 1: 24 mg (three 8-mg tablets once daily) for 2 weeks, rest 1 week

- 33 patients were enrolled into **Cohort 1** under original protocol.

Cohort 2: 16 mg (two 8-mg tablets once daily) continuous dosing

- Safety Data Review: Rate of Grade 3 or greater AEs of special interest (ie, diarrhea, skin rash, stomatitis) that are identified after the first 6 patients and again after 12 patients have completed **Cycle 1**:
  - **>33%:** Stop **Cohort 2** (≥3 of 6 patients or ≥5 of 12 patients with Grade 3 or greater AEs of special interest) and begin **Cohort 3**.
  - **≤33%:** Keep enrolling **Cohort 2** until 30 patients are enrolled and treated and no additional patients will be enrolled.
- 34 patients were enrolled into **Cohort 2** under Amendment 1 or Amendment 2.

Cohort 3: 12 mg (one 8-mg tablet and two 2-mg tablet once daily) continuous dosing

- Only if **Cohort 2** is stopped due to toxicity.
- No patient was enrolled into **Cohort 3**.

Toxicity are assessed based on the grade of the adverse events using CTCAE Version 4.03.

All treatments are taken orally, once daily (QD) at approximately the same time each morning. On Day 1 of each cycle, the patient's absolute neutrophil count (ANC) must be $\geq 1.5 \times 10^9$/L and platelet count must be $\geq 100 \times 10^9$/L before administering the next dose of poziotinib. For Cycle 1 only, the ANC and platelet levels should also be confirmed prior to the dose on Day 8. Day 1 of a new cycle is equivalent to Day 22 of the previous cycle, with a window of ±3 days for the visit. If a visit is delayed during 1 cycle, then all subsequent cycles will be delayed sequentially.

All treated patients will be followed up until disease progression, death, intolerable adverse events or up to a maximum of 24 months whichever comes earlier.

3.1 Sample Size Considerations

Other important treatments for HER2-positive MBC include T-DM1, lapatinib-capecitabine combination, and neratinib. Published ORRs reported for these regimens are 43.6%, 30.8%, and 24%, respectively [1-3]. The purpose of this study is to evaluate the safety and efficacy of poziotinib and identify the optimal dose for future clinical development.

The original protocol included test of hypotheses with a sample size of 70 as described below. For the primary endpoint of **ORR** in a single-arm study, to test the null hypothesis (hypothesis of no interest in the study) of 24% (P0=0.24) vs. the alternative hypothesis (hypothesis of interest in the study) of 42% (P1=0.42), a sample size of 70 patients achieves 88% power to detect a difference (P1-P0) of 0.18 using a two sided binomial test. The target significance level is 0.05. The actual significance level achieved by this test is 0.0345. These results assume that the population proportion under the null hypothesis is P0=0.24.

In Amendment 1, two lower dose cohorts were added to determine the optimal dose regimen. The test of hypotheses was removed, and the study became a proof-of-concept study. A

sample size of 30 was proposed for **Cohort 2.** If **Cohort 2** was stopped due to toxicity, a sample size of 20 patients was proposed for **Cohort 3.**

3.2 Randomization

This study is not randomized. Patients will be enrolled sequentially. The enrollment of Cohort 2 starts after enrollment of Cohort 1 is complete.

3.3 Tumor Assessments

Tumor assessment must be performed by Investigators using computed tomography (CT) or magnetic resonance imaging (MRI) at **Screening** up to 30 days prior to **Cycle 1**, **Day** 1. Imaging studies performed prior to the signing of Informed Consent as part of the site's routine standard of practice are allowed at the discretion of the Sponsor.

Tumor assessments will be performed every 6 weeks (±14 days) until disease progression, death, intolerable adverse events, or for up to 24 months.

Each subsequent tumor assessments must use the same Baseline radiologic technique, either CT or MRI. Response evaluation will be performed using RECIST criteria, Version 1.1 **[4].** For radiographic assessment, CT or MRI must be performed at every assessment.

Measurable and non-measurable lesions that will not be followed by radiological methods should be documented appropriately.

3.3.1 Baseline Tumor Assessments

Tumor assessment and measurement at baseline as well as post-baseline will follow the RECIST v1.1 criteria and will be evaluated by the local Principal Investigators. At Baseline tumor assessment, up to 5 measurable lesions (maximum of 2 lesions per organ) representable of all involved organs will be identified as **target lesions**. Target non-nodal tumor lesions (TLs) should have longest diameter ≥10mm and can be measured reproducibly. Target lymph nodes (LNs) should have short axis ≥15mm. The sum of diameters (SOD), which is the sum of the longest diameter of all target TLs and the short axis of all target LNs, will be calculated as the reference baseline value for tumor response evaluation later in the study.

All the other TLs, pathological LNs (short axis ≥10mm), and lesions not measurable by CT or MRI will be identified as **non-target lesions** and the size of these lesions are not recorded for the purpose of follow-up.

3.3.2 Follow-up Tumor Assessments

Target lesions are followed by tumor size, longest diameter of TLs and short axis of LNs, and SOD are calculated for response evaluation. At each tumor assessment, the tumor response of **target lesions** is determined as below.

- **Complete Response (CR)**: disappearance of all target TLs and all target LNs with short axis <10mm
- **Partial Response (PR)**: ≥30% decrease in SOD from **Baseline**, and not PD (see below)
- **Progressive Disease (PD)**: ≥20% increase in SOD from previous smallest SOD on study, and an absolute increase of ≥5mm
- **Stable Disease (SD)**: SOD change neither sufficient for PR nor sufficient for PD
- **Not Evaluable (NE)**: not all target lesions evaluated, and evaluated lesions not sufficient for PD

Non-target lesions are assessed qualitatively with present, absent or unequivocal progression and tumor response is determined as below.

- **Complete Response (CR)**: disappearance of all non-target TLs, normalization of tumor marker level, and all non-target LNs with short axis <10mm
- **Non-CR/Non-PD**: persistence of any non-target lesion and/or maintenance of abnormal tumor marker level
- **Progressive Disease (PD)**: unequivocal progression (substantial worsening) of existing non-target lesions
- **Not Evaluable (NE)**: not all non-target lesions evaluated
- **Not Applicable (NA)**: no non-target lesions identified at **Baseline**

New lesions are tumor lesions that were not present at **Baseline**. The finding of a new lesion should be unequivocal, and the appearance of new malignant lesions denotes disease progression.

3.3.3 Time Point Response at Each Tumor Assessment

As summarized below, the time point response at each follow-up tumor assessment are determined according to the evaluation of target lesions, non-target lesions, and new lesions.

Table 1. Determination of Time Point Response

Target Lesions	Non-Target Lesions	New Lesions	Time Point Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Any but PD	No	
SD	Any but PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	
Any	Any	Yes[1]	
NE	Any but PD	No	NE

[1] If the finding of new lesion is equivocal, it should be confirmed from next scan.

4 ANALYSIS POPULATIONS

Two analysis populations have been defined as follows:

- The **Evaluable Population (EP)** consists of all patients who are enrolled, complete at least one cycle of poziotinib treatment, and have at least one evaluable post-baseline tumor response evaluation using RECIST criteria, Version 1.1.
- The **Safety Analysis Population (SAF)** includes all patients who signed informed consent, enrolled, and received at least one dose of study treatment. All demographics, Baseline characteristics, and safety data will be analyzed using the **SAF** population.

5 STATISTICAL METHODS OF ANALYSIS

5.1 General Principles

The statistical analyses will be reported using summary tables, figures, and data listings. All analyses and tabulations will be performed using SAS® Version 9.3 or higher. All tables, listings, and figures will be validated and reviewed before being finalized.

In summary tables of continuous variables, the minimum and maximum will be presented to the same number of decimal places as the original data. The mean, median, and 95% confidence interval (CI) will be presented to one more decimal place than the original data. The standard deviation (SD) and standard error (SE) will be presented to two more decimal place than the original data.

In summary tables of categorical variables, count and percentage will be provided. In general, percentage values are to be presented to whole number if sample size ≤100; to one decimal place if sample size is between 100 and 1000; and to two decimal places if sample size is greater than 1000. Any test of comparison performed will be 2-sided at 5% level of significance unless otherwise specified.

5.1.1 Definition of Baseline Values

Baseline values will be defined as the most recent non-missing measurements collected prior to the first dose of poziotinib. If there is more than one value on or before the date of the first dose of poziotinib, the values closest to and prior to (including on) the date of the first dose will be used as the baseline value. Change from baseline will be defined as post-baseline value minus baseline value.

5.1.2 Handling of Missing Data

Missing data will be not imputed.

5.1.3 Pooling of Centers

Data from different centers will be combined for the purpose of the analysis. The number of patients enrolled will be presented by study site.

5.1.4 Interim Analysis

There will be no formal interim analysis specified or conducted in this study. The data will be periodically reviewed for quality and completion.

5.1.5 Testing/Validation Plan

SAS® Version 9.3 or higher on the Windows system will be used for creation of Tables, Listings, and Figures. All tables, listings, and figures will be validated and reviewed before being finalized. Independent programming will be conducted to verify tables and listings as appropriate. Tables will be reviewed for accuracy, consistency with this plan, consistency within tables, and consistency with corresponding outputs.

5.2 Background Characteristics

All background characteristics will be summarized by cohort and for all patients. Corresponding patient data listings will be provided.

5.2.1 Patient Disposition

Disposition of patients will be summarized for all enrolled patients. The summary data will include number (%) of patients in SAF, in EP, and who completed the study (i.e., treatment for 24 months). The reasons for treatment discontinuation and study discontinuation will also be summarized.

5.2.2 Protocol Deviation

The following important protocol deviations will be summarized with count and percentage.

- Patients entered the study even though they did not satisfy the entry criteria.
- Patients developed withdrawal criteria during the study but were not withdrawn.
- Patients received the wrong treatment or incorrect dose.
- Patients received an excluded concomitant treatment.

All protocol deviations will be provided in patient data listings.

5.2.3 Demographic and Baseline Characteristics

Demographics and other baseline disease characteristics will be summarized using descriptive statistics. The summary will include, but will not be limited to, age (as continuous and categorical [<65, ≥65 and <75, ≥75]), gender, ethnicity, race, height, weight, body mass index,

ECOG performance status, staging, hormone receptor status, prior HER2 therapy and prior cancer therapy (surgery, radiation and chemotherapy).

5.2.4 Medical History

Medical history information will only be provided in patient data listings.

5.2.5 Concomitant Medication

A concomitant medication will be defined as any medication that was taken either on the day of or after the administration of the first dose of poziotinib through the end of the study. This includes medications that started prior to the initiation of the first dose of poziotinib if the patient continues using it.

For all concomitant medications, counts and percentages of patients will be presented by medication class and preferred name coded by the World Health Organization Drug dictionary (WHODrug Enhanced SEP-2015 B2). Patients with more than one medication of the same medication class or preferred name will be counted only once. Patient data listings will be provided.

5.3 Efficacy Analyses

All efficacy endpoints will be analyzed based on the Evaluable Population for each cohort.

5.3.1 Best Overall Response

Since there is no statistical test of hypotheses in this proof-of-concept study, the overall responses will be provided using various criteria or assessment. The determination of time point overall response will be made by the local site investigator using RECIST criteria, Version 1.1. The determination of best overall response (BOR) will be summarized as below.

1. Per Investigator Assessment: BOR will be summarized as reported by the local investigator. This includes CR, PR, SD, PD or NE. Please note the following:
   - Spectrum will not cross-check or derive the responses based on tumor measurement or time point responses as all BOR will be as reported by the investigator.
   - Local Investigator may not report a CR or PR as confirmed or unconfirmed, or SD adjudicated based on the duration of treatment and will be reported as is.
2. Per Sponsor Derivation: Spectrum will use the detailed tumor data as reported on case report form such as tumor measurements, lesion assessment, duration of treatment, and confirmation scan to derive the time point response and BOR using RECIST criteria, Version 1.1.
   - Time point response will be determined as described in Section 3.3.2 and 3.3.3.
   - BOR with confirmation will be determined as described in Table 2 below.

- BOR without confirmation will not require a confirmation scan for CR/PR or ≥6 weeks on-treatment.
- If there is a time point with missing tumor measurement, but the time point response is available from site, this time point response will be used for determination of BOR regardless of missing tumor measurement.

Table 1. Determination of Confirmed Best Overall Response

Initial Best Response (can start at any visit)	Response at Subsequent Visit	Best Overall Response
CR	CR[1]	CR
PR	PR[2] or unconfirmed CR[2]	PR
PR	SD (not followed by CR/PR)	SD
SD	SD or unconfirmed CR/PR	SD
CR or PR or SD	PD	SD[3] or PD[4]
CR or PR or SD	NE (no additional evaluable visit)	SD[3] or NE[4]
PD	Any	PD
NE	NE (no additional evaluable visit)	NE

[1] Confirmation scan needs to be ≥4 weeks from previous scan, 1 intervening NE is allowed.
[2] Confirmation scan needs to be ≥4 weeks from previous scan, 1 intervening NE/SD is allowed.
[3] If initial CR/PR/SD is ≥6 weeks on-treatment.
[4] If initial CR/PR/SD is <6 weeks on-treatment.

5.3.2 Primary Efficacy Endpoint

Objective Response Rate (ORR)

ORR is the proportion of patients whose BOR is CR or PR. Various ORRs, based on Per Investigator Assessment BOR, Per Sponsor Derivation BOR with confirmation, and Per Sponsor Derivation BOR without confirmation as described in Section 5.3.1, will be estimated using count, percentage and exact (Clopper-Pearson) 95% CI.

5.3.3 Secondary Efficacy Endpoints

Progression-Free Survival (PFS)

PFS is defined as the number of months from the treatment start date to the date of documented disease progression or death due to any cause. PFS of living patients without documented PD will be censored at the time of last tumor assessment or the date of first treatment if there is no post-baseline tumor assessment.

Distribution of PFS will be estimated using the Kaplan-Meier method in the Evaluable Population. The median and quartiles of PFS and the PFS rate at 3, 6, 9 and 12 months will be reported with corresponding 95% CI.

Disease Control Rate (DCR)

DCR is the proportion of patients whose BOR is CR, PR, or SD. Various DCRs, based on Per Investigator Assessment BOR, Per Sponsor Derivation BOR with confirmation, and Per Sponsor Derivation BOR without confirmation as described in Section 5.3.1, will be estimated using count, percentage and exact (Clopper-Pearson) 95% CI.

Time to Progression (TTP)

TTP is defined as the number of months from the first dose of study drug to tumor progression, which excludes death without tumor progression, by the end of study. TTP of patients who die without documented PD will be censored at date of death. TTP of living patients without documented PD is censored at the same time as PFS, which is the last tumor assessment or the date of first treatment if there is no post-baseline tumor assessment.

Distribution of TTP will be estimated using the Kaplan-Meier method in the Evaluable Population. The median and quartiles of TTP and the TTP rate at 3, 6, 9 and 12 months will be reported with corresponding 95% CI.

Duration of Response (DoR)

DoR will be evaluated only for patients whose BOR is CR or PR and is defined as the time (in months) from the date that response evaluation criteria are first met for CR or PR (whichever status is recorded first) until the first subsequent date that PD or death is documented. DoR of patients without documented PD or death will be censored at the time of last tumor assessment.

Distribution of various DoRs will be estimated using the Kaplan-Meier method. The median and quartiles of DoR and the DoR rate at 3, 6, 9 and 12 months will be reported with corresponding 95% CI.

5.3.4 Subgroup Analysis

Analysis of the primary and selected secondary efficacy endpoints will be performed for the following subgroups:

- patients by total lines of prior therapy (2 lines, 3 lines, >=4 lines);
- patients who received prior treatment of pertuzumab in addition to trastuzumab and T-DM1;
- patients who received at least one prior treatment with tyrosine kinase inhibitor (TKI) for HER2 (lapatinib and neratinib).

5.4 Safety Analyses

All safe analyses will be reported based on the Safety Population for each cohort.

5.4.1 Drug Exposure

The extent of exposure to poziotinib will be summarized with descriptive statistics using the following parameters:

- Duration of treatment: number of days between first dose and last dose of poziotinib, inclusive (i.e. days difference between first dose and last dose +1).
- Number of cycles treated
- Days of treatment administered
- Relative dose intensity (RDI): the percentage of planned dose that each patient actually received during the study. The planned dose is defined as the dose that would be given if no doses were missed and no dose reductions were made for the number of cycles (28 days per cycle) for the duration of treatment regardless of the number of cycles actually administered. Thus,

  $$\text{RDI} = 100 * \frac{\text{total dose administered}}{336 * \left[\text{integer of}\left(\frac{\text{days difference between first dose and last dose}}{21}\right) + 1\right]}$$

- Last dose level: the last dose is assumed to be the lowest dose level prescribed by investigator
- Number of dose reduction
- Number and percentage of patients with no reduction, or with dose reduction to 16mg (Cohort 1 only), 12mg, 10mg and 8mg.
- Study day of first dose reduction
- Study day and duration of first drug interruption

5.4.2 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. All AEs that occur from the first dose of study treatment through 35 (±5) days after the last dose of study treatment is administered will be recorded on the AE CRF. From the time the study Informed Consent is signed through the first dose of study drug administration, only serious AEs (SAEs) that are related to study procedures will be recorded.

AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA, Version 18.0) and will be classified by MedDRA system organ class (SOC) and preferred term (PT). All AEs will be classified for severity by the Investigator according to the definitions set forth by the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03).

All AE tables will be presented with number and percentage of patients. AE listings will include patient ID, gender, age, race, AE verbatim term and preferred term, AE start date and end date,

AE duration, CTCAE grade, if the AE is SAE or not, relation to study drug, study drug action, outcome, and if treatment is given.

Only treatment-emergent AEs (TEAE), as defined in Section 5.4.2.2, will be summarized in tables. SAEs reported prior to treatment but after informed consent will only be provided in AE listings.

5.4.2.1 Overall Summary

An overall summary table of TEAEs will be provided. The summary will include any TEAE, TEAE by severity, any treatment-related AE, treatment-related AE by severity, SAEs, and AEs leading to study drug discontinuation.

5.4.2.2 Treatment Emergent Adverse Events

TEAEs are AEs that occur from the first dose of study treatment until 35 (±5) days after the last dose of study treatment. If it cannot be determined whether an AE is treatment-emergent (based on start date or, if the start date is missing then based on the stop date), then the AE will be considered treatment-emergent.

Summary of TEAEs by MedDRA SOC and PT will be presented in a separate table with any grade and with Grade 3 or 4. Patients who experience more than one type of AE will be counted under each of the corresponding PTs. Patients who experience different episodes of the same AE will be counted only once under the corresponding PT. Similarly, for determination of MedDRA SOC incidences, patients who experience multiple AEs under the same SOC will be counted only once for that SOC. Listing of all TEAEs will also be provided.

5.4.2.3 Treatment-Related Adverse Events

Assessment of relatedness to study drug for all AEs will be classified by investigators and reported. “Definitely related”, “probably related” and “possibly related” AEs will be considered as treatment related. An AE will be assigned as treatment-related if the relationship to study drug is missing.

The incidences of treatment-related AEs will be presented by MedDRA SOC and PT with any grade and with Grade 3 or 4.

5.4.2.4 Serious Adverse Events

SAEs are defined (21 CFR 312.32, ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use E2A Guideline) as those AEs that meet any of the following criteria:

- Results in death.

- Is life-threatening: ie, any event that, in the opinion of the Investigator, poses an immediate risk of death from that event.
- Requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalizations for study therapy, disease-related procedures, or placement of an indwelling catheter, unless associated with other SAEs).
- Results in a persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Includes important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in this definition.

Listing of all SAEs will be provided. Treatment-emergent SAEs and treatment-related SAEs will be summarized by MedDRA SOC and PT with any grade and with Grade 3 or 4.

5.4.2.5 Maximum Severity of Adverse Events

TEAEs and treatment-related AEs will be summarized by MedDRA SOC, PT, and maximum CTCAE severity grade. AEs with a missing severity grade will not be included in these analyses. Patients who experience the same event at more than one severity level will be counted only once under the maximum severity level. The overall adverse event incidences will also be presented in these tables as a reference.

5.4.2.6 Other Important Adverse Events

AEs leading to death and study drug discontinuation will be presented in separate listings and the incidence will be summarized in the overall summary of TEAE table.

5.4.2.7 Adverse Events of Special Interest

Summary of TEAEs, treatment-related AEs, and SAEs for diarrhea, rash, stomatitis, and pneumonitis by MedDRA PT will be provided in separate tables with any grade and with Grade 3 or 4. Study day of first incidence for diarrhea, rash, and stomatitis will be summarized using median and range. Rash of special interest will be reported as collective of multiple PTs related to rash, including rash, dermatitis acneiform, rash maculo-papular, etc. Similarly, stomatitis of special interest will be reported as collective of multiple PTs related to stomatitis, including stomatitis and mucosal inflammation.

5.4.3 Laboratory Parameters

Clinical laboratory samples will be collected at screening and throughout the study. The clinical laboratory values will be classified according to the NCI CTCAE Version 4.03. Tables of shifts in severity and in clinical abnormality from baseline to worst post-baseline on study, for key laboratory parameters, will be provided.

5.4.4 Vital Sign Data

A summary of raw values and changes from baseline values will be provided at each scheduled time point for the following measurements: body temperature, systolic and diastolic blood pressure, and heart rate. A listing of all values will also be included.

5.4.5 ECOG Performance Status

Descriptive statistics will be presented for ECOG scores at baseline. The number and percentage of patients with shifts from baseline ECOG score (0, 1, or 2) to the worst post-baseline ECOG score (0, 1, 2, 3, or 4) will be summarized.

5.4.6 Cardiac Assessment

Cardiac assessment will be provided in the data listings.

6 REFERENCES

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