Statistical Analysis Supplemental Plan (sSAP)

MK-7119 Protocol No. 001-08

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1 INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2 SUMMARY OF CHANGES

sSAP Version	Protocol Number	Section	Description of Change	Rationale
1	001-04			
2	001-05	All sections	South Korea and Taiwan were included to participate in this study, and the primary analysis is pre-specified to perform in Japanese population of response evaluable set. Analyses will be also conducted in all participants population, i.e., population which include participants enrolled in Japan, South Korea and Taiwan.	To provide supplemental data for marketing application in each country.
3	001-07	3.1 Determination of Sample Size	The number of participants in the main cohort in Japanese population was changed from 50 to 38.	Due to change in clinical practice, feasibility of the trial was reassessed.
		3.3.4 Participant Characteristics	Details in participants characteristics for summary was added.	Updated referring to the tables provided in HER2CLIMB clinical study report.
		3.3.2.8 Examination of Subgroup	Definition of presence or history of brain metastases was added.	Updated referring to HER2CLIMB statistical analysis plan.
		3.3.9.1 Extent of Exposure	Definition of extent of exposure was added.	Updated referring to HER2CLIMB statistical analysis plan.
			Absolute dose intensity relative dose intensity will be summarized as deemed necessary.	Reflected comments from clinicals.
		All sections	Typographical errors and redundancies were corrected, and clarifications were made.	
4	001-08	3.3.2.8 Examination of Subgroup	A few subgroup analyses were added.	Reflected the subgroup used in the previous studies
		3.3.4 Participant Characteristics	A few characteristics were added.	Included the characteristics used in subgroup analysis
		3.3.7 Efficacy Analyses	Analysis set for PFS and OS included the all treated participants set in the main study.	Aligned with the comment from the agency.

3 DATA ANALYSIS METHODS

The primary objective of this study is to assess ORR of tucatinib in combination with trastuzumab and capecitabine by independent central review (ICR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in Japanese population, hence, the primary analysis population of the endpoint is the response evaluable set as defined in the section 3.3.2.7 but only includes Japanese participants. All of the analyses, i.e., efficacy endpoints, safety endpoints as well as demographics and other baseline characteristics, will be performed in Japanese population. These analyses will also be conducted in all participants population, i.e., population which include participants enrolled in Japan, South Korea and Taiwan.

Key elements of the statistical analysis plan are summarized below.

Study Design Overview	A phase 2 open-label, single arm study of MK-7119 in combination with trastuzumab and capecitabine in participants with previously treated locally advanced unresectable or metastatic HER2+ breast carcinoma
Primary Objective	• Assess ORR of tucatinib in combination with trastuzumab and capecitabine by ICR per RECIST v1.1 in Japanese population.
Secondary Objectives	• Assess ORR of tucatinib in combination with trastuzumab and capecitabine by ICR per RECIST v1.1 in all participants population. • Assess ORR of tucatinib in combination with trastuzumab and capecitabine per RECIST v1.1 by investigator assessment (INV) in Japanese population and all participants population. • Assess the duration of response (DOR) of tucatinib in combination with trastuzumab and capecitabine by ICR and INV per RECIST v1.1 in Japanese population and all participants population. • Assess the progression free survival (PFS) of tucatinib in combination with trastuzumab and capecitabine by ICR and INV per RECIST v1.1 in Japanese population and all participants population. • Assess the overall survival (OS) of tucatinib in combination with trastuzumab and capecitabine in Japanese population and all participants population. • Assess the safety of tucatinib in combination with trastuzumab and capecitabine in Japanese population and all participants population.
Treatment Assignment	This is an open label, single-arm study and no randomization/blinding will be performed.
Analysis Populations	Efficacy: Response evaluable set for ORR and DOR All treated participants set for PFS and OS Safety: All treated participants set
Primary Endpoint	Confirmed ORR (cORR) by ICR per RECIST v1.1. in Japanese population
Key Secondary Endpoints	• cORR by ICR per RECIST v1.1. in all participants population • cORR by INV per RECIST v1.1 in Japanese population and all participants population

	• DOR by ICR and INV per RECIST v1.1 in Japanese population and all participants population • PFS by ICR and INV per RECIST v1.1 in Japanese population and all participants population • OS in Japanese population and all participants population • Safety parameters: AEs, laboratory parameters and vital signs in Japanese population and all participants population
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	Using the Clopper-Pearson method, the primary efficacy analysis will be performed by testing the null hypothesis of cORR being less than or equal to 20% against the alternative hypothesis that cORR is greater than 20% at 1-sided 5% level of significance.
Statistical Methods for Key Safety Analyses	Safety and tolerability will be descriptively assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, vital signs, and ECG measurements.
Interim Analyses	There are no planned interim analyses for this study.
Multiplicity	No multiple comparisons are planned and no alpha adjustment is needed because only 1 primary endpoint will be tested in this single arm study.
Sample Size and Power	The primary efficacy analysis will be performed based on the participants enrolled on the main portion of the trial in Japan. With approximately 38 participants, the study will have 80% power to detect a 20% increase in ORR from 20% to 40% and 90% power to detect a 25% increase in ORR from 20% to 45%, at one-sided significance level of 0.05. A total of approximately 13 participants from South Korea and Taiwan are planned to be enrolled at this time.

3.1 Determination of Sample Size

The study is designed to estimate the confirmed objective response rate (cORR) in Japanese population and to detect an improvement in the ORR compared with a historical 20% response rate. The rationale for the historical response rate is based on the observed response rate from the control arm of HER2CLIMB trial and responses of patients treated with drug therapy after multiple treatment lines of anthracyclines, taxanes, trastuzumab, pertuzumab or T-DM1 (Murthy 2020; Yokoe 2021; Masuda 2020; Charles 2006).

Approximately 42 participants will be enrolled in Japan, including 4 participants in safety run-in. The primary efficacy analysis will be performed based on the participants enrolled on the main portion of the trial. With approximately 38 participants, the study will have 80% power to detect a 20% increase in ORR from 20% to 40% and 90% power to detect a 25% increase in ORR from 20% to 45%, at one-sided significance level of 0.05, based on exact methods using EAST®, Version 6.0, by Cytel Inc.

On 02-Aug-2021 the SMC conducted an evaluation of overall safety after 4 Japanese participants were enrolled in the safety run-in and the safety and tolerability was deemed acceptable by the SMC; hence the enrollment of the safety run-in was completed and that of the main study was initiated on the following day.

A total of approximately 13 participants from South Korea and Taiwan are planned to be enrolled.

3.2 Study Endpoint Definitions

3.2.1 Objective Response Rate

The primary endpoint in this study is the cORR by ICR. The ORR is defined as the proportion of participants with confirmed complete response (CR) or partial response (PR), per RECIST v1.1. Only response assessments before first documented PD or new anti-cancer therapies will be considered. Participants with missing data are considered non-responders.

3.2.2 Duration of Response

Duration of response (DOR) is defined as the time from the first objective response (CR or PR that is subsequently confirmed) to documented PD per RECIST v1.1 or death from any cause, whichever occurs first. Only those who achieve a confirmed response will be included in the analysis.

3.2.3 Progression Free Survival

Progression free survival (PFS) time is defined as the time from the first date of study treatment to the date of documented disease progression using RECIST v1.1 or death from any cause, whichever occurs first. Participants who are alive and have not progressed at the time of the analysis will be censored at the time of their last tumor assessment documenting absence of PD. Participants lacking an evaluation of tumor response after their start of study treatment will have their event time censored at 1 day.

3.2.4 Overall Survival

Overall survival (OS) is defined as the time from start of study treatment to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the participant is known to be alive. Participants lacking data beyond their start of study treatment will have their survival time censored at 1 day.

3.3 Statistical and Analytical Plans

3.3.1 Responsibility

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This study including both the safety run-in and the main study is being conducted as a non-randomized, open-label study, i.e., participants, investigators, and SPONSOR personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

3.3.2 General Considerations

In general, descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages (of non-missing) per category for categorical variables.

The 2-sided 90% exact CI using Clopper-Pearson method (Clopper 1934) will be calculated for the response rates.

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 90% will be calculated based on the complementary log-log transformation (Collett 1994).

3.3.2.1 Randomization and Blinding

Randomization and blinding will not be performed.

3.3.2.2 Adjustments for Covariates

No adjustment for covariates is planned in the analyses.

3.3.2.3 Handling of Dropouts and Missing Data

Please refer to 3.3.7.1. Primary Efficacy Endpoint and 3.3.7.2 Secondary Efficacy endpoints for handling of dropouts and missing data.

3.3.2.4 Multicenter Studies

This study will be conducted at multiple study centers; however, it is not anticipated that any center will accrue enough participants to warrant an analysis by center.

3.3.2.5 Multiple Comparisons and Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed because only 1 primary endpoint will be tested in this single arm study.

3.3.2.6 Data Transformations and Derivations

Time variables based on 2 dates, e.g., start date and end date, will be calculated as (end date – start date + 1 [in days]). Details of data transformations and derivations are as follows:

- Baseline: The last non-missing observation prior to or on the first dose of study treatment (tucatinib, capecitabine or trastuzumab), unless otherwise specified. If more than one assessment meet the above criteria and were collected on the same date, the value of the assessment indicating better status will be used as baseline to be conservative, for instance, lower vs. higher lab grade, ECOG 0 vs. 1, ECG normal vs. abnormal. If there are no directional difference (for instance, lab values of the same grade) of observation on the same date, the last record in database (identified by sequence number or visit number) will be marked as baseline.
- Pre-treatment Period: Prior to first dose of study treatment (tucatinib, capecitabine or trastuzumab)
- Study Treatment Period: Period of time that begins on the date of the first dose of study treatment (tucatinib, capecitabine or trastuzumab) through 30 days after the date of the final dose of study treatment (tucatinib, capecitabine or trastuzumab).
- Study Day:

  Safety: Study day will be calculated for safety endpoints relative to the first dose of study treatment (tucatinib, capecitabine or trastuzumab). The first dose of study treatment will be Day 1, and the date preceding Day 1 will be Day –1.

  Efficacy: Study day will be calculated for efficacy endpoints relative to the date of the first dose of treatment. The day of the first dose of treatment will be Day 1.

3.3.2.7 Analysis Sets

The all treated participants set, response evaluable set, safety run-in set and PK analysis set are defined below.

The all treated participants set will include all participants who receive any amount of study drug. Safety, PFS, and OS will be analyzed using this analysis set.

Response evaluable set will include all participants who meet all following criteria: (1) had measurable disease at baseline, (2) received any amount of study treatment, and (3) had at least one post baseline disease assessment or discontinued due to clinical progression, toxicity, or death. ORR will be analyzed using the response evaluable analysis set.

Safety run-in set will include all participants who were treated during the safety run-in period and meet the safety evaluable criteria as defined in the protocol section 3.1. Dose limiting toxicity (DLT) information will be summarized for this analysis set.

The PK analysis set will include all participants in the safety set from whom at least one post-baseline PK assessment was reported. The PK analysis set will be used for PK analysis.

Japanese population is defined as Japanese participants enrolled in Japanese sites in the respective data sets. All participants population include all participants enrolled in Japan, South Korea and Taiwan.

3.3.2.8 Examination of Subgroups

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed below.

- Age: <65 vs. ≥65 years
- ECOG: 0 vs. 1 as recorded in eCRF at baseline
- Hormone Receptor Status (Negative, Positive): Patients 'positive' for either or both estrogen receptor and progesterone receptor will be assigned to the 'positive' subgroup. Patients 'negative' for both receptors will be assigned to the 'negative' subgroup.
- Brain metastasis at baseline (yes, no): Patients with brain metastasis at baseline or who have a history of brain metastases will be assigned to the 'Yes' subgroup. Participants with dural lesions only, i.e. no parenchymal brain lesions, will be assigned to the 'No' subgroup
- Number of prior lines of systemic therapy in the metastatic setting: 2L vs. 3L+
- Visceral disease at baseline (yes, no): Patients with metastasis except breast, bone, chest wall, lymph nodes muscle, skin and soft tissue will be assigned to the 'Yes' subgroup. Otherwise, patients will be assigned to the 'No' subgroup.
- Prior trastuzumab deruxtecan treatment: Yes vs. No

3.3.2.9 Timing of Analyses

The primary analysis will be conducted when all of the treated participants in Japanese population have been followed for at least 8 months (or all responders have been followed for a minimum of 6 months after their initial response, whichever comes first), have discontinued from the study, or had 30 days safety follow-up after disease progression, whichever comes first. In addition, for the purpose of regulatory submission in South Korea and Taiwan, the additional analyses may be conducted subsequently to the initial analysis.

3.3.3 Participant Disposition

An accounting of study participants by disposition will be tabulated and the number of participants in each analysis set will be summarized.

The table will present the number and percentage of participants who were enrolled, received study drug, and participated in follow-up visits. The number and percentage of patients who discontinued treatment will be summarized by the reason for treatment discontinuation. The number and percentage of participants who discontinued the study will be summarized by the primary reason for study discontinuation.

Number of screen failures and the percentage relative to the total number of subjects screened will be summarized.

3.3.4 Participant Characteristics

Demographics and other baseline characteristics will be summarized using counts and percentages for categorical variables and summary statistics (mean, median, standard deviation, and range) for continuous variables. Characteristics to be summarized include the following:

- Demographic variables: age, sex, race, ethnicity
- ECOG performance status (0, 1)
- Disease history:
    - Time (months) from the initial diagnosis of breast cancer to study entry
    - Time (months) from metastatic diagnosis including metastases to study entry
    - Disease status at study entry (Locally advanced, unresectable, Metastatic/Recurrent and Metastatic)
    - Estrogen/progesterone receptor status (Positive for ER or PR or both, Negative for ER and PR, other)
    - Overall stage at initial diagnosis (0-III, IV)
    - History of brain metastases or brain metastases at study entry (not including participants with history or presence of dural lesions only)
    - Number of prior lines of systemic therapy
    - Number of prior lines of systemic therapy in the metastatic setting
    - Histology of current diagnosis (Invasive ductal carcinoma, Invasive lobular carcinoma, Invasive ductal/lobular carcinoma, and so on)
    - Location of metastases
    - Visceral disease at baseline

    Applicable to the patients with Brain metastases

    - Brain metastases treatment status at baseline (not including participants with history or presence of dural lesions only)
    - Time from the last surgery for brain metastases to study entry (months)
    - Time from 1st diagnosis of brain metastases to study entry (months)

- Prior surgery and/or radiotherapy for brain metastases (yes, no)

- Prior trastuzumab deruxtecan treatment

3.3.5 Treatment Compliance

Treatment administration will be summarized for safety analysis set. Summary statistics for duration of treatment (weeks) and the number of cycles per participant will be presented. See 3.3.9.1.

3.3.6 Subsequent anticancer treatment

The type and regimen of subsequent anticancer treatment after discontinuation from study treatment will be summarized or listed as appropriate.

3.3.7 Efficacy Analyses

Table 1 summarizes the analysis approach for primary and secondary efficacy endpoints. Efficacy analyses will be performed in Japanese population and all participants population of the respective analysis sets.

Table 1 Analysis Strategy for Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method‡	Analysis Population	Missing Data Approach
Primary Endpoint				
cORR by ICR	P	90% exact CI by Clopper-Pearson Method	response evaluable set in the main study in Japanese population	participants with missing data= non-responder
cORR by ICR	S	90% exact CI by Clopper-Pearson Method	response evaluable set in the safety run-in and main study in Japanese population	participants with missing data= non-responder
Secondary Endpoints/Hypotheses				
Secondary Endpoint				
cORR by ICR	P	90% exact CI by Clopper-Pearson Method	response evaluable set in the main study in all participants population	

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method‡	Analysis Population	Missing Data Approach
cORR by INV	P	90% exact CI by Clopper-Pearson Method	response evaluable set in the main study in Japanese population and all participants population	participants with missing data= non-responder
DOR by ICR and INV	P	Kaplan-Meier estimate of median survival time	response evaluable set in the main study in Japanese population and all participants population §	
PFS by ICR and INV	P	Kaplan-Meier estimate of median survival time	all treated participants set in the main study in Japanese population and all participants population	
OS	P	Kaplan-Meier estimate of median survival time	all treated participants set in the main study in Japanese population and all participants population	

† P=Primary approach; S=Supportive approach.
‡ Statistical models are described in further detail below.
§ Only participants with objective response will be included.
ICR: independent central review; INV: investigator assessment; cORR: confirmed objective response rate; DOR: duration of response; PFS: progression-free survival; OS: overall survival

3.3.7.1 Primary Efficacy Analyses

Since the primary objective of this study is to assess ORR in Japanese population, the primary analysis will be conducted in Japanese population of the response evaluable set. Analyses of ORR in all participants population are conducted as a secondary endpoint.

The primary endpoint in this study is the cORR by ICR in the response evaluable set in Japanese population. The cORR is defined as the proportion of participants with confirmed complete response (CR) or partial response (PR), per RECIST v1.1. Only response assessments before first documented PD or new anti-cancer therapies will be considered. The participants in response evaluable set who are enrolled in the main study, i.e., after safety run-in period will be used for the primary efficacy analysis. Participants with missing data are considered non-responders.

The cORR by ICR and its exact 2-sided 90% CI using the Clopper-Pearson method (Clopper 1934) will be calculated.

The primary efficacy analysis will be performed by testing the null hypothesis of cORR being less than or equal to 20% against the alternative hypothesis that cORR is greater than 20% at overall 1-sided 5% level of significance, i.e., H0: $P \leq 0.20$ vs. Ha: $P > 0.20$.

The study will be considered positive if the lower bound of the 2-sided 90% exact Clopper-Pearson CI for cORR is greater than 20%, so that the null hypothesis that the cORR is less than or equal to 20% can be rejected.

In addition, all participants in response evaluable set which includes participants in safety run-in period will be used as supportive analysis, which includes participants who are enrolled in both the safety run-in and main study periods.

3.3.7.2 Secondary Efficacy Analyses

cORR by ICR in all participants population will be analyzed using the same method as for the primary endpoint.

3.3.7.2.1 Objective Response Rate by INV

cORR by INV will be analyzed in the response evaluable set who are enrolled in the main study using the same method as the primary endpoint.

3.3.7.2.2 Duration of Response

DOR by ICR and INV will be summarized descriptively using Kaplan-Meier method and Kaplan-Meier plots will be provided in the response evaluable set who are enrolled in the main study. Only those who achieve a confirmed response will be included in the analysis. The censoring rules for DOR is provided in Table 2.

Table 2 Censoring Rules for DOR and PFS

Situation	Date of Progression or Censoring	Outcome
No post-tumor assessments after the first objective response	Date of the first objective response	Censor
No progression nor death, no new anti-cancer therapy initiated	Date of last tumor assessment of CR, PR, SD, or non-CR/non-PD	Censor
No progression nor death, new anti-cancer therapy initiated	Date of last CR, PR, SD, or non-CR/non-PD on or prior to date of new anti-cancer therapy	Censor
New anti-cancer therapy started before PD or death observed	Date of last CR, PR, SD, or non-CR/non-PD on or prior to date of new anti-cancer therapy	Censor
Death or progression after ≤ 1 missed tumor assessments	PD or death	End of response (Event)
Death or progression right after two or more consecutive missed tumor assessments	Date of last tumor assessment of CR, PR, SD, or non-CR/non-PD	Censor
A missed tumor assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. For PFS, "No post-tumor assessments after the first objective response" will be substituted with "No post-baseline assessments" and "the first objective response" with "the first dose of treatment."		

3.3.7.2.3 Progression-free survival

PFS per ICR and INV will be summarized descriptively using Kaplan-Meier method and Kaplan-Meier plots will be provided in the all treated participants set in the main study. Subjects who are alive and have not progressed at the time of the analysis will be censored at the time of their last tumor assessment that was a CR, PR, non-CR/non-PD or SD. Details of the censoring scheme for the analysis of PFS are described below in Table 2.

3.3.7.2.4 Overall Survival

OS will be summarized descriptively using Kaplan-Meier method and Kaplan-Meier plots will be provided in the all treated participants set in the main study. Subjects who did not achieve the event (death) at the time of the analysis or are lost to follow-up will be censored at the date they were last known to be alive.

3.3.8 Pharmacokinetic Analyses

Individual (participant) plasma tucatinib concentrations at each sampling time will be listed and summarized with descriptive statistics. Additional exploratory PK analyses may be conducted, including exploratory analyses investigating the relationship between tucatinib exposure and efficacy and safety endpoints. Summaries by ethnicity (Japanese and Korean) may be provided as appropriate. These analyses will be described in a separate PK analysis plan.

3.3.9 Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, vital signs, and ECG measurements. Safety analysis will be performed in Japanese population as well as all participants population of the all treated participants set

3.3.9.1 Extent of Exposure

Exposure will be summarized by treatment arm using counts and percentages for categorical variables and summary statistics (mean, median, standard deviation, and range) for continuous variables.

The following information will be summarized separately for tucatinib, capecitabine, and trastuzumab:

- Total number of treatment cycles per subject
- Duration of exposure
    - For tucatinib, duration of exposure (days) = date of last dose – date of first dose + 1
    - For capecitabine, duration of exposure (days) = (date of last dose +7) – date of first dose) + 1
    - For trastuzumab, duration of exposure (days) = (date of last dose +20) – date of first dose) + 1

Absolute dose intensity (ADI) for tucatinib and capecitabine and relative dose intensity (RDI) may be summarized as deemed necessary, and total dose, intended does intensity (IDI), absolute dose intensity (ADI) and relative does intensity (RDI) will be defined as below.

- Total Dose of tucatinib (mg), capecitabine (mg/m^2), and trastuzumab (mg/kg):

  Total dose (units) = $\sum_{i=1}^{n}(dose_i)$, where i = dose number, $dose_i = i^{th}$dose received (units), n = total number of doses received

- Intended dose intensity (IDI): the intended dose of drug per unit of time (day).

  For example, tucatinib: IDI = 300mg BID =600 (mg/day); capecitabine: IDI = 2000 mg/m^2/day x (14 dosing day/21 days in a cycle) =1333.3 mg/m^2/day

- Absolute dose intensity (ADI): the actual dose per unit of time that the subject received over the duration of exposure for that study drug.

  ADI = Total dose / Duration of exposure (days)

- Relative dose intensity (RDI): the percent of the intended dose intensity over the entire treatment period:

RDI = ADI/IDI x 100%

3.3.9.2 Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, grade 3 and higher AEs, SAEs, treatment-related SAEs, AEs leading to deaths, and AEs leading to study treatment discontinuation. Treatment-emergent adverse events and treatment-related adverse events are defined as follows:

- Treatment-emergent adverse events (TEAE): Treatment-emergent AEs are defined as events that are new or worsened on or after receiving the first dose of study treatment (tucatinib, capecitabine or trastuzumab) and up through 30 days after the last dose of tucatinib.
- Treatment-related adverse events: Adverse events assessed by the Investigator as 'related' to tucatinib, capecitabine, trastuzumab, or any of these treatments.

AEs will be listed and summarized by Medical Dictionary for Regulatory Activities (MedDRA), preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in 1 participant, the AE will be counted once as the occurrence.

Summaries to be produced include:

- Incidence of TEAE by SOC and preferred term
- Incidence of TEAE by decreasing frequency of preferred term
- Incidence of TEAE by toxicity grade, SOC and preferred term
- Incidence of grade 3 or higher of TEAE by decreasing frequency of preferred term
- Incidence of TEAEs which lead to premature discontinuation of study treatment by decreasing frequency of preferred term
- Incidence of TEAEs which lead to dose interruption or dose reduction of study treatment by decreasing frequency of preferred term
- Incidence of treatment related TEAEs by decreasing frequency of preferred term

DLTs will be listed and summarized for the participants in the safety run-in period.

3.3.9.3 Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed. The following summaries of SAEs will be produced.

- Incidence of treatment emergent SAEs (TESAEs) by decreasing frequency of preferred term
- Incidence of TESAEs by decreasing frequency of SOC and preferred term
- Incidence of treatment related TESAEs by decreasing frequency of preferred term
- Incidence of TEAEs which lead to death by decreasing frequency of preferred term

3.3.9.4 Clinical Laboratory Results

For laboratory results, summary statistics for maximum post baseline toxicity grades and for change from baseline may be tabulated as appropriate. Laboratory values will be listed with grade per NCI CTCAE v4.03 and flagged when values are outside the normal reference range.

In addition, the incidence of liver abnormalities will be summarized. A liver abnormality is defined as AST or ALT elevations that are >3 x ULN with concurrent elevation of total bilirubin >2 x the ULN.

3.3.9.5 Other Safety Analyses

The frequency and percentage of participants with post-baseline clinically significant vital signs will be summarized. The clinically significant vital signs are defined as heart rate >100 bpm; Temperature >38.0 degrees C and respiratory rate >20 breaths per min. Blood pressure will be summarized both for subjects with systolic blood pressure >120 mmHg or diastolic blood pressure >80 mmHg, as well as for subjects with systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg. For weight, the maximum decrease from baseline will also be summarized.

Abnormal physical examination findings may be collected as AEs. ECOG performance status will be listed.

For cardiac ejection fraction the minimal post baseline ejection fraction and the maximum decrease from baseline will be summarized.

3.4 References

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