1.0 Title Page

Statistical Analysis Plan

Study M14-359

A Randomized, Open-Label, Multicenter, Phase 3 Trial Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice of Standard Chemotherapy in Subjects Receiving First Cytotoxic Chemotherapy for Metastatic or Advanced Non-Squamous Non-Small-Cell Lung Cancer (NSCLC) and Who Are Current or Former Smokers

Date: 06 Nov 2019

Version 4.0

2.0 Table of Contents

List of Tables

2.1 Summary of Versions

Version	Date of Completion	Summary
1.0	29 July 2016	First finalized version
2.0	31 July 2018	Second finalized version submitting to FDA for review at pre-NDA meeting
3.0	24 May 2019	Third finalized version incorporating FDA's feedback
4.0	06 Nov 2019	• Clarified the LSP subgroup definitions • Added assumed median OS for sample size calculation to address FDA's comment • Added summary for tissue sample disposition and LSP assay results in the patient disposition section

2.2 List of Abbreviations and Definition of terms

Abbreviation	Term
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
AST	As Treated
BID	Twice a Day
C	Cycle
CI	Confidence Interval
CR	Complete Response
CRF or eCRF	Case Report Form or Electronic Case Report Form
D	Day
DNA	Deoxyribonucleic Acid
DOR	Duration of overall response
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	European Quality of Life-5 Dimensions
FACT	Functional Assessment of Cancer Therapy
HR	Hazard ratio
IRT	Interactive Response Technology
ITT	Intent-To-Treat
LSP	Lung Subtype Panel
LSP+	Lung Subtype Panel positive
LSP-	Lung Subtype Panel negative
NSCLC	Non-small cell lung cancer
NCI CTCAE	National Cancer Institute Common Terminology Criteria For Adverse Events
NFLSI-17	NCCN-Functional Assessment of Cancer Therapy (FACT) Lung Symptom Index-17
ORR	Objective response rate
OS	Overall survival
PARP	Poly-(ADP-ribose)-Polymerase
PD	Pharmacodynamic or Progressive Disease
PR	Partial response
PT	Preferred term
QoL	Quality of Life
SAE	Serious adverse event

SAP	Statistics analysis plan
SOC	System organ class
TEAE	Treatment emergent adverse event
VAS	Visual analog scale

3.0 Introduction

Veliparib is a potent Poly-(ADP-ribose)-Polymerase (PARP) inhibitor that inhibits the repair of Deoxyribonucleic Acid (DNA) damage induced by chemotherapeutics. Veliparib increases sensitivity of tumor cells to DNA-damaging agents in vitro and in vivo. It has been shown to inhibit PARP in murine tumors experimental models in vivo. In addition, in clinical trials, veliparib has been shown to inhibit PARP in tumors in humans.

Phase 1 and preliminary Phase 2 study data suggest the addition of veliparib to carboplatin and paclitaxel may improve progression free survival (PFS) and overall survival (OS) in patients with advanced or metastatic non-squamous non-small cell lung cancer (NSCLC). Therefore, this study (Study M14-359) is being conducted to assess efficacy and toxicity of veliparib in combination with carboplatin and paclitaxel versus investigator's choice of standard chemotherapy in subjects with metastatic or advanced non-squamous NSCLC receiving first cytotoxic chemotherapy and who are current or former smokers. In addition, exploratory biomarker analysis from Phase 2 Study M10-898 and Phase 3 Study M11-089 showed OS benefit from veliparib treatment in Lung Subtype Panel (LSP) positive (LSP+) subjects, based on research assay conducted at Washington University. Therefore, this study will assess efficacy and safety in LSP+ subjects.

This statistical analysis plan (SAP) provides details to further elaborate statistical methods as outlined in Clinical Study Protocol M14-359 incorporating Amendments 1, 2, 3, and 4 and describes analysis conventions to guide the statistical programming. LSP status will be based on results of LSP assay developed in partnership with Qiagen (may also be referred to as LSA or LP52). LSP status (LSP positive, LSP negative and LSP unknown) will be defined based on all analytically valid results from up to two repeat assay runs (maximum of 3 runs including initial testing). However, please note that SAP should not be impacted regardless of which LSP assay method applied. Analyses will be performed using SAS® Version 9.3 (SAS Institute, Inc., Cary, NC) or later under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objective of the study is to assess if the addition of oral veliparib to carboplatin and paclitaxel in subjects who are metastatic or advanced NSCLC and have LSP+ biomarker will improve OS versus investigator's choice of platinum doublet standard chemotherapy.

The secondary objectives of the study are to assess PFS in LSP+ subjects, objective response rate (ORR) in LSP+ subjects, OS in all subjects, PFS in all subjects, and ORR in all subjects. The tertiary objectives are to assess duration of overall response (DOR), Quality of Life (QoL), and ECOG performance status in LSP+ subjects and all subjects.

4.2 Design Diagram

This is a Phase 3, randomized, open-label multicenter study to assess efficacy, safety and tolerability of veliparib plus carboplatin and paclitaxel versus investigator's choice of platinum doublet standard chemotherapy in subjects receiving first cytotoxic chemotherapy for documented metastatic or advanced non-squamous NSCLC and who are current or former smokers. The study is designed to enroll approximately 525 subjects at approximately 150 sites. The enrollment is completed with 595 subjects randomized in this study.

Subjects will be randomized in a 1:1 ratio using Interactive Response Technology (IRT) into one of the two treatment arms:

Arm A: veliparib 120 mg BID and carboplatin (AUC 6 mg/mL/min)/paclitaxel (200 mg/m^2)

Arm B: investigators' choice of platinum doublet chemotherapy (carboplatin/paclitaxel, cisplatin/pemetrexed, or carboplatin/pemetrexed)

Subject randomization will be stratified by investigators' preferred platinum doublet chemotherapy (carboplatin/paclitaxel versus cisplatin/pemetrexed versus carboplatin/pemetrexed), smoking status (current smoker versus former smoker), ECOG performance status (0 versus 1) and gender (male versus female).

The dose schedules for both groups of the study are detailed below in Table 1 and Table 2.

Table 1. Treatment Schema for Each Cycle for Veliparib and Carboplatin/Paclitaxel Treatment Group

Days*	1	2	3	4	5	6	7	8 – 21
Veliparib	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	Twice a day	
Paclitaxel			Once					
Carboplatin			Once					

Note: Day 1 and Day 2 of veliparib is labeled as Day –2 and Day –1 (pre-dose) in the protocol. Day 3, the start of Paclitaxel and Carboplatin, is labeled as Day 1 in the protocol. Day 1 for each cycle is calculated from start of veliparib in the analyses.

Table 2. Treatment Schema for Each Cycle for Investigators' Choice of Platinum Doublet Chemotherapy

Days	1	2	3	4	5	6	7	8 – 21
Carboplatin/Paclitaxel	Once							
Cisplatin/Pemetrexed	Once							
Carboplatin/Pemetrexed	Once							

Subjects will receive veliparib 120 mg BID in combination with carboplatin/paclitaxel or investigators' choice of platinum doublet chemotherapy for up to a maximum 6 cycles of treatment. This interval is defined as the platinum-based treatment period. After 6 cycles of platinum doublet chemotherapy, investigators may elect to administer maintenance pemetrexed in the post first line setting regardless of which therapy their subjects are randomized to receive. This interval is defined as maintenance period. All subjects will remain on study until reaching a protocol-defined event of disease progression.

Study visits and assessments (except for tumor assessment) will be performed on the day of chemotherapy administration in each cycle until the subject reaches a radiographic progression or prematurely discontinue. Tumor assessment will be performed at baseline, Cycle 3 Day 1 and Cycle 5 Day 1. After cessation of first line platinum doublet therapy, tumor assessments will be performed every 9 (q9) weeks until 1 year after the 1st dose of veliparib (or beyond 1 year until maintenance therapy is discontinued), then q12 weeks until radiographic progression or death. After the determination of first radiographic progression, subjects no longer undergoing clinical assessments will have survival information reported via the Electronic Case Report Form (eCRF) at two-month intervals (or as requested by sponsor to support data analysis) beginning at the last clinical assessment and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study.

The detail of study schedule can be found in Figure 1 of the protocol (Study Schedule Schematic).

4.3 Sample Size

Sample size calculation for the original protocol:

Assuming the true hazard ratio of OS in favor of the veliparib 120 mg BID + carboplatin/paclitaxel treatment group is 0.64 in current smokers, a total of 210 OS events will be needed for the study to have at least 90% power at one-sided α level of 0.025 to detect a statistically significant treatment effect in current smokers for the veliparib 120 mg BID + carboplatin/paclitaxel group using the log rank test for OS. A total of approximately 300 current smokers will be enrolled to acquire the 210 death events.

During the enrollment period for approximately 300 current smokers, it is anticipated that approximately 225 former smokers will be enrolled concurrently. Assuming the true hazard ratio (HR) of OS in favor of the veliparib 120 mg BID + carboplatin/paclitaxel treatment group is 0.71 in the whole population (current plus former smokers), a total of 369 OS events will be needed for the study to have approximately 90% power at

one-sided α level of 0.025 to detect a statistically significant treatment effect in the whole population for the veliparib 120 mg BID + carboplatin/paclitaxel group using the log rank test for OS.

Sample size consideration for OS analysis in LSP+ subgroup:

Among subjects classified as LSP+ (based on research assay) in Study M10-898, it was noted that there was an improvement in overall survival in the veliparib in combination with carboplatin and paclitaxel group compared to the carboplatin and paclitaxel alone. This finding was later confirmed by a subset of the sampled population from the Phase 3 NSCLC squamous Study M11-089. Based on the meaningful clinical benefit of veliparib treatment observed retrospectively in the LSP+ (based on research assay) subset of subjects from Study M10-898 and Study M11-089 collectively, the primary analysis population in Study M14-359 has been changed from OS in the current smoker population to OS in the biomarker defined LSP+ (based on Qiagen assay) population.

Based on 452 subjects having tissue samples (assumed 76% LSP sample availability rate, out of 595 enrolled subjects), Table 3 below provides the power and number of events (assuming 80% event rate at final analysis) for a range of likely LSP+ (based on Qiagen assay) rates if the treatment ratio is 1:1 in the LSP+ group and true HR of OS is 0.65 in LSP+ subgroup.

Table 3. Summary of Estimated Number of Events and Power in LSP+ Subjects

Number of LSP+ Subjects (LSP+ rate)	Number of Events in LSP+	Power in LSP+ Subgroup (one-sided alpha = 0.025)
271 (60%)	216	89%
226 (50%)	180	82%
180 (40%)	144	73%

Median OS of 11.3 – 13.9 months have been reported in the literature for the control treatment in populations similar to the ITT population.[1-3] An expected median OS in

LSP+ patients in a similar patient population is not available due to very limited clinical outcomes data in this patient population from Study M10-898 and external sources.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Study populations that will be involved in analyses are defined as follows:

- Intent-To-Treat (ITT) population - all subjects who are randomized by IRT. The data from ITT population will be analyzed by the treatment group assignment given at the time of randomization, even if the subject takes the incorrect drugs that do not match the assigned treatment, or does not receive any treatment, or does not follow the protocol until completion.
- As Treated (AST) population – all subjects who are randomized by IRT and take at least 1 dose of study drug (veliparib/investigators' choice of standard chemotherapy) as assigned treatment given at time of randomization.
- LSP subgroup - ITT and AST population definition are also applied to LSP+, LSP-, unknown LSP. Note that unknown LSP status pools two subgroups:
  - subjects without available samples and
  - subjects with samples, which either did not run based on quality or quantity of assay input material, or which ran but did not render a positive or negative analytically valid result based on up to 2 repeat runs.

5.2 Variables Used for Stratification of Randomization

Subject randomization is stratified by investigators' preferred platinum therapy (carboplatin/paclitaxel, cisplatin/pemetrexed, and carboplatin/pemetrexed), smoking status (current smoker, former smoker), ECOG performance status (0, 1) and gender (male, female).

Smoking status was a stratification factor at randomization for overall population per protocol. However, based on the evidence provided by Study M11-089 and Study M10-898, smoking status is not a significant prognostic factor in this patient

population. Therefore, smoking status is excluded from stratified efficacy analysis even though it was a stratification factor at randomization.

6.0 Analysis Conventions

General Considerations

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a two-sided *P* value ≤ 0.05. The date of randomization is defined as the date that the IRT issues a randomization number.

Definition of Platinum-doublet Study Drug

Unless otherwise specified, the platinum-based study drug in this document refers to veliparib plus carboplatin and paclitaxel or investigators' choice of standard chemotherapy for up to 6 cycles.

Definition of Post-Platinum-doublet Study Drug

Unless otherwise specified, the post-platinum-based study drug in this document refers to pemetrexed maintenance after veliparib plus carboplatin/paclitaxel or investigator's choice of standard chemotherapy (carboplatin/paclitaxel, cisplatin/pemetrexed, and carboplatin/pemetrexed) for up to 6 cycles.

Definition of Post-Treatment Therapy (new anti-cancer therapy)

Unless otherwise specified, the post-treatment therapy (excluding surgical and radiation therapy) in this document refers to the therapy after veliparib plus carboplatin/paclitaxel or investigator's choice of standard chemotherapy (carboplatin/paclitaxel, cisplatin/pemetrexed, and carboplatin/pemetrexed) or after pemetrexed maintenance.

Pemetrexed maintenance is not considered as post-treatment therapy.

Dealing with Multiple Values on the Same Day

In cases where multiple values are collected on the same day (including baseline visit and post-baseline visits), the maximum grade value will be selected as the value for that day in the shift analyses of laboratory parameters; the worst symptom value will be selected as the value for that day in the mean change from baseline in quality of Life (European Quality of Life-5 Dimensions (EQ-5D-5L), NCCN-Functional Assessment of Cancer Therapy (FACT) Lung Symptom Index-17 (NFLSI-17)) and mean change from baseline in performance status (ECOG). In the analyses of change from baseline in laboratory and vital signs parameters, the arithmetic average will be calculated and used as the value for the day which multiple values are collected on the same day.

Definition of Baseline

Unless otherwise specified, the baseline is defined as the last non-missing observation collected on or prior to the date of the first dose of study drug (veliparib plus carboplatin and paclitaxel or investigators' choice of standard chemotherapy) for treated subjects (or the date of randomization for non-treated subjects).

Definition of Final Observation (Platinum-doublet Study Drug)

For laboratory and vital signs variables, Final Observation is defined as the last non-missing observation collected within 30 days following the last dose of platinum-based study drug (veliparib plus carboplatin and paclitaxel or investigators' choice of standard chemotherapy).

Definition of Cycle Rx Days in Each Cycle

Cycle Rx Days for each cycle are calculated for each time point relative to first dose of veliparib or investigators' choice of standard chemotherapy/carboplatin/paclitaxel in each cycle.

Definition of Analysis Windows

All time points and corresponding time windows are defined for each cycle based on Cycle Rx Day 1 to obtain number of days relative to the Cycle Rx Day 1 of each cycle.

For visit-wise longitudinal analyses such as change from baseline to all post-baseline assessments in EQ-5D-5L, NFLSI-17, ECOG, laboratory, and vital signs values, the time windows specified in Table 4 and Table 5 describe how the data will be assigned to the protocol specified visits. Analysis time windows are constructed using the following algorithm:

- Determine the nominal Cycle Rx Day for each scheduled visit.
- Determine the window around a specific nominal Cycle Rx Day as in Table 4 and Table 5.
- If more than one assessment is included in a time window, the assessment closest to the nominal day should be used. If there are two observations equally distant to the nominal day, the later one will be used in analyses.

Table 4. Time Windows for Visit-Wise Analysis (Laboratory, and Vital Signs)

Scheduled Visit	Nominal Cycle Rx Day/	Time Window
Cycle 1 Day 1	BASELINE	As baseline definition
Cycle 1 Day 15[(1)]	17	(14, 20)
Cycle X Day 1	1	(–7, 7)

(1) For Chemistry and Hematology only.

Table 5. Time Windows for Visit-Wise Analysis (EQ-5D-5L, NFLSI-17, ECOG)

Scheduled Visit	Nominal Cycle Rx Day	Time Window
Cycle 1 Day 1	BASELINE	As baseline definition
Cycle 1 Day 15	17	(14, 20)
Cycle X Day 1	1	(–7, 7)
Post Platinum Doublet Visit X(1)	1	(–10, 10)
Pemetrexed Maintenance therapy Visit X(2)	1	(–10, 10)
Post Pemetrexed Maintenance therapy Visit X(3)	1	(–10, 10)

(1) For EQ-5D-5L, NFLSI-17, and ECOG, nominal Cycle Rx Day 1 for Post Platinum Doublet Visit will be generated as 21 days from the study drug end date before Pemetrexed maintenance therapy if subjects receive Pemetrexed maintenance therapy or 21 days from study drug end date if subjects don't receive Pemetrexed maintenance therapy.

(2) During maintenance therapy, nominal Maintenance Visit X will be generated as 60 days from Day 1 of the first maintenance therapy for EQ-5D-5L, NFLSI-17, and ECOG.

(3) Post Maintenance Visit X will be generated as 60 days from the last date of maintenance therapy for EQ-5D-5L, NFLSI-17, and ECOG.

Chemistry Laboratory Platform Change

ICON Inc is the central laboratory used in this study. The chemistry platform will be transitioned from the Roche Diagnostics Hitachi Modular System (old) to the Abbott Architecture (new) in December 2015 while the study is expected to be still on-going. The chemistry data obtained from the old chemistry platform will be converted to the new chemistry platform and the converted data will be combined with the data obtained from the new system for all statistical analysis and the normal ranges associated with the new chemistry platform will be applied. The analysis of mean changes from baseline shifts above and below the normal ranges, the flagging of potentially clinically significant (PCS) laboratory data, and the Common Terminology Criteria for Adverse Events (CTCAE) grading of chemistry labs will be performed as if all the chemistry data were generated by one platform – the new chemistry platform.

7.0 Demographics, Baseline Characteristics, Medical History, Prior/Concomitant Medications, Prior Oncology Therapies and Post-Treatment Medication

ITT population will be used in the analyses of demographic, baseline characteristics, medical history, and prior/concomitant medication, prior oncology therapy for adjuvant, neo-adjuvant, metastatic, surgical, or radiation therapies and post-treatment medication.

There are 5 treatment groups to be displayed for all analyses: veliparib 120 mg BID + carboplatin + paclitaxel, each of investigator's choice of platinum doublet therapy group (carboplatin + paclitaxel, cisplatin + pemetrexed, carboplatin + pemetrexed), and overall investigator's choice of platinum doublet therapy group.

The data will be summarized for LSP+ subjects, LSP- subjects, LSP unknown status, and all subjects by each treatment group unless otherwise specified.

7.1 Demographic and Baseline Characteristics

Categorical demographic and baseline characteristic variables will be summarized with the number and percentage of subjects. The number of subjects with missing information will also be summarized. Continuous variables will be summarized with mean, standard deviation, median, minimum and maximum. There will be no statistical comparison for the demographic and baseline characteristics.

Continuous demographic variables include age, baseline height and weight. Categorical demographic variables include gender, age category (< 65 versus ≥ 65 years), race (White, Black, Asian, Other), and region 1 (Japan, US and western EU and Australia and Canada, Eastern EU/Russia, Other Asia).

US and western EU and Australia and Canada Region include Australia, Austria, Argentina, Brazil, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Mexico, Netherlands, New Zealand, Norway, Portugal, Puerto Rico, South Africa, Spain, Sweden, Switzerland, United Kingdom, United States, and Canada.

Eastern Europe/Russia includes Belarus, Croatia, Czech Republic, Egypt, Estonia, Hungary, Israel, Latvia, Lithuania, Poland, Russia, Serbia, Slovakia, Turkey, and Ukraine.

Continuous baseline characteristics include average pack years smoking exposure, baseline tumor burden (based on the sum of baseline target lesion sizes (mm)), time from diagnosis to first dose of study drug, time from tissue obtained for LSP (if available) and/or histology (if available) to first dose of study drug.

Categorical baseline characteristics include:

- Smoking status (current smoker versus former smoker)
- Investigators' preferred platinum doublet therapy (carboplatin/paclitaxel versus cisplatin/pemetrexed versus carboplatin/pemetrexed)
- ECOG (0 versus 1)
- Number of Involved Organ Sites from baseline Tumor Assessment (1 – 2 versus > 2) and type of organ (e.g., lung, liver etc)
- Site of biopsy (if data is available)
- Reported differentiation status (if data is available)

Smoking status definition can be found in Protocol Section 8.3.

In addition, demographic and baseline characteristics will also be summarized by stratification variables under which subjects are randomized in IRT.

7.2 Medical History

Medical history data will be summarized and presented using System Organ Class (SOC and Preferred Terms (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The SOCs will be presented in alphabetical order and the PTs will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular PT will be summarized for LSP+ subjects and all subjects by each treatment group. Subjects reporting more than one PT within a SOC will be counted

only once for that SOC. The data will be summarized for LSP+ subjects and all subjects by each treatment group. There will be no statistical comparison for the medical history.

7.3 Prior/Concomitant Medications, Prior Oncology Therapies and Post-Treatment Medications

A prior medication is defined as any medication taken prior to the date of the first dose of study drug (Veliparib or investigators' preferred platinum therapy). A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken on or after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug. A post-treatment medication for the treatment of oncology is defined as any medication taken after veliparib plus carboplatin/paclitaxel or investigator's choice of standard chemotherapy (carboplatin/paclitaxel, cisplatin/pemetrexed, or carboplatin/pemetrexed) or after pemetrexed maintenance and entered as "Post Treatment Therapy" on the eCRF excluding surgical and radiation therapy. Pemetrexed maintenance is not considered as post-treatment medication.

The number and percentage of subjects taking prior medications, concomitant medications, and post-treatment medications will be summarized by the generic name coded by WHO dictionary. The number and percentage of subjects who have prior oncology therapies will be summarized by regimen names and treatment setting (adjuvant, neoadjuvant, metastatic). In addition, the best response of any therapies prior to study drug (or randomization for non-treated subjects) will be summarized. The data will be summarized for LSP+ subjects and all subjects by each treatment group. There will be no statistical comparison for the prior medications, prior oncology therapies, concomitant medications, and post-treatment medications.

8.0 Subject Disposition

Analyses for the subject disposition will be performed on ITT population. The data will be summarized for LSP+ subjects, LSP- subjects, LSP unknown status, and all subjects, by each treatment group.

The screen failure reasons will be summarized for the screen failure subjects. The number of randomized subjects, the number of treated subjects, and the number of subjects in the maintenance pemetrexed will be summarized by country and investigator.

The number and percentage of subjects who discontinue study and study drug will be summarized. All reasons and the primary reason for discontinuation will be included in the summary. There will be no formal statistical comparison for the subject disposition.

In addition, summary of LSP status would be provided with the following information:

- Number of subjects with no sample for LSP status evaluation
- Number of subjects with sample available for LSP status evaluation
  - Number of subjects for whom sample did not run
  - Number of subjects for which sample ran but with no positive or negative result (QC fail)
  - Number of subjects for whom sample ran but with positive or negative result (QC pass)
    - Number subjects with LSP positive status
    - Number of subjects with LSP negative status

9.0 Study Drug and Maintenance Drug Exposure

Analyses for the study drug and maintenance drug exposure will be performed on AST population. The summary will include two parts: the exposure to study drug during platinum doublet therapy period and the exposure to pemetrexed during the maintenance treatment period. The data will be summarized for LSP+ subjects, LSP- subjects, LSP unknown status, and all subjects, by each treatment group.

9.1 Exposure to study drug during platinum doublet therapy period

Duration of veliparib exposure is defined as total number of days a subject received veliparib. Average dosed days per cycle of veliparib is defined as total number of days a

subject received veliparib divided by the number of cycles that subject were exposed to veliparib. Descriptive statistics (mean, standard deviation, median, and range) will be used to summarize study drug exposure. In addition, the number and percentage of subjects exposed to veliparib will be summarized for each of the following 7-day duration intervals.

- 1 to 7 days
- 8 to 14 days
- 15 to 21 days
- 22 to 28 days
- 29 to 35 days
- 36 to 42 days
- > 42 days

The average number of cycles that subjects were exposed to veliparib, carboplatin, paclitaxel, cisplatin and pemetrexed will be summarized.

The numbers and percentages of subjects having dose reduction of veliparib, carboplatin, paclitaxel, cisplatin, and pemetrexed will be summarized. If a subject has any dose reduction from the previous dose, this subject will be considered as having experienced dose reduction. All AST subjects will be included in the summary.

The numbers and percentages of subjects having dose delay of carboplatin, paclitaxel, cisplatin, and pemetrexed will be summarized. If the elapsed time between two consecutive doses of platinum doublet therapy (carboplatin, paclitaxel, cisplatin, and pemetrexed) is more than 27 days, the subject will be considered as having experienced a dose delay of platinum doublet therapy. Subjects who take only one cycle of platinum doublet therapy will not be included in this summary.

Dose Intensity of veliparib is defined as the ratio of actual total veliparib dose and the planned total veliparib dose. Each planned cycle length for veliparib is 21 days. The planned cycles for veliparib include the cycles before veliparib is discontinued.

Dose Intensity of veliparib for each subject = actual total veliparib dose in all cycles/(240 mg *7 days *number of planned cycles for veliparib)

Dose intensity will also be calculated for carboplatin, cisplatin, paclitaxel and pemetrexed as defined in Table 6.

Table 6. Dose Intensity for platinum doublet of chemotherapy

	Actual total Dose	Planned total Dose	Dose Intensity (%)
Carboplatin	Actual total dose AUC (mg/mL/min)	AUC 6 (mg/mL/min) * total number cycles of carboplatin	100*actual total dose/Planned total dose
Paclitaxel	Actual total dose (mg/m^2)	200 mg/m^2 * total number of cycles of paclitaxel	100*actual total dose/Planned total dose
Cisplatin	Actual total dose (mg/m^2)	75 mg/m^2 * total number of cycles of cisplatin	100*actual total dose/Planned total dose
Pemetrexed	Actual total dose (mg/m^2)	500 mg/m^2 *total number of cycles of pemetrexed	100*actual total dose/Planned total dose

9.2 Exposure to maintenance pemetrexed

The number and percentage of subjects exposed to maintenance pemetrexed treatment will be summarized.

10.0 Efficacy Analyses

10.1 General Considerations

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a two-sided *P* value ≤ 0.05 (when rounded to three decimal places).

When LSP status is obtained by the Qiagen assay for all submitted tissue samples (LSP positive, LSP negative, LSP unknown), the date of EDC data cutoff will be determined and there will be a final LSP data transferred and database will be locked. For overall survival (OS) and response/progression related efficacy endpoints (PFS, ORR, DOR, best response rate (BRR), depth of response (DpR), QoL), the same cutoff date will be used as the primary endpoint (OS in LSP+ subjects).

All efficacy endpoints will be analyzed for LSP+, LSP-, LSP unknown and all subjects unless otherwise specified. The date of randomization is defined as the date when the randomization number is issued by IRT. Pemetrexed maintenance period is included in efficacy analyses.

There will be 5 treatment groups presented in efficacy analyses: veliparib 120 mg BID + carboplatin + paclitaxel, each of investigator's choice of platinum doublet therapy group (carboplatin + paclitaxel, cisplatin + pemetrexed, carboplatin + pemetrexed), and overall investigator's choice of platinum doublet therapy group. Statistical comparison will be between the two randomized treatment groups (veliparib 120 mg BID + carboplatin + paclitaxel versus overall investigator's choice of platinum doublet therapy).

If a subject starts Post-Treatment Therapy as described in Section 6.0, then all data except death for this subject measured on or after the start date of Post-Treatment Therapy (excluding surgical and radiation therapy) will not be used for PFS, ORR, BRR, DOR, DpR, ECOG, and QoL analyses, unless otherwise specified.

10.2 Primary Efficacy Analysis

The primary efficacy analysis will be a comparison of overall survival (OS) distributions between the two randomized treatment groups in LSP+ subjects, using the log-rank test, stratified by ECOG performance status, investigators' preferred platinum therapy, and gender. The balance of treatment groups in each stratum will be checked before conducting the stratified analysis. The hazard ratio and corresponding 95% CI between the two randomized treatment groups in LSP+ subjects will also be obtained using the covariate adjusted Cox Proportional Hazard Model with covariates being ECOG performance status, investigators' preferred platinum therapy, and gender. In addition, the median survival time with the corresponding 95% CI as well as the survival rates at Month 12, 18 and 24 will be provided from Kaplan-Meier estimation.

OS for a given subject will be defined as the number of days from the date that the subject is randomized to the date of the subject's death. All events of death on or prior to the

"Cutoff" date will be included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject has not died on or before the "Cutoff" date, and there is any data (survival follow-up, study visit, death date, etc.) confirming that the subject is still alive or dies after the "Cutoff" date, the data will be censored at the "Cutoff" date; otherwise the data will be censored at the date when the subject was last known to be alive.

10.3 Secondary Efficacy Analyses

Fixed sequence testing procedure[4] is used for analyses of the primary and secondary efficacy endpoints to control for the familywise error rate (FWER). If veliparib plus carboplatin/paclitaxel treatment group is not statistically significantly better than the investigators' choice of standard therapy group for the primary efficacy endpoint of OS in LSP+ subjects, then statistical significance will not be declared for any of the secondary efficacy endpoints, regardless of the observed *P* values. *P* values for the secondary efficacy analyses will be subject to multiple comparison adjustments using the fixed sequence testing method, with the analyses performed in the following order: PFS in LSP+ subjects, ORR in LSP+ subjects, OS in all subjects, PFS in all subjects, and ORR in all subjects.

10.3.1 Progression-Free Survival in LSP+ subjects

PFS for a given subject will be defined as the number of days from the date that the subject was randomized to the date the subject experiences an event of disease progression or to the date of death (all causes of mortality) if disease progression is not reached. All events of disease progression occurring on or before the "Cutoff" date will be included, regardless of whether the event occurred while the subject was still taking study drug or had discontinued study drug. However, if a disease progression event occurred immediately after that subject missed more than one scheduled consecutive disease progression assessments (e.g., the disease progression event occurred more than 182 days (24 weeks + 14 days) after the last disease progression assessment), this subject will be censored at the last disease progression assessment prior to the disease progression

event. All events of death occurring on or before the "Cutoff" date will be included for subjects who had not experienced disease progression provided the death occurred within 84 days (12 weeks) of the last disease progression assessment. If the subject does not have an event of disease progression nor has the subject died on or before the "Cutoff" date, the subject's data will be censored at the date of the subject's last disease progression assessment on or before the "Cutoff" date. The two thresholds here, 182 days and 84 days, were evaluated based on the time schedule for tumor assessment. If the randomized subject did not have any post-baseline disease progression assessment, the subject's data will be censored on the date of randomization. If the result of disease progression assessment is 'unevaluable', this disease progression assessment is not included in the analyses.

The median PFS time with the corresponding 95% CI will be provided from Kaplan-Meier estimation for each treatment group in LSP+ subjects and compared between two randomized treatment groups using the log-rank test, stratified by ECOG performance status, investigators' preferred platinum therapy, and gender. The hazard ratio and corresponding 95% CI between the two randomized treatment groups will also be obtained using the covariate adjusted Cox Proportional Hazard Model with covariates being ECOG performance status, investigators' preferred platinum therapy, and gender. In addition, progression free rates at Month 6, 12, and 18 will be provided from Kaplan-Meier estimation.

10.3.2 Objective Response Rate in LSP+ Subjects

ORR is defined as the proportion of subjects with complete response (CR) or partial response (PR) per RECIST (version 1.1). Confirmation is required to determine objective response. Confirmation rules are as follows:

Confirmed CR: After the first tumor assessment showing CR, the CR will be considered as confirmed if the very next tumor assessment also shows CR (with no other responses in between), and if the duration between the two CRs is greater than or equal to 28 days.

Confirmed PR: After the first tumor assessment showing PR, the PR will be considered as confirmed if a subsequent tumor assessment also shows CR/PR (irrespective of tumor assessment in between that shows stable disease) and if the duration of the first PR and the next CR/PR is greater than or equal to 28 days.

Data after the first appearance of progressive disease (PD) will not be included since responses after PD may be due to other non-study drug influences (e.g., post-treatment therapy).

The ORR will be estimated and compared between the two randomized treatment groups using covariate adjusted logistic regression with the covariates being ECOG performance status, investigators' preferred platinum therapy, and gender. In addition, 95% confidence interval will be constructed for the estimated proportion and the odds ratio of ORR and corresponding 95% CI between two randomized treatment groups will be estimated.

BRR (best response rate) in LSP+ subjects will also be summarized for each treatment group, with BRR defined as the best response in all post-baseline disease assessments in the following order: complete response, partial response, stable disease, progressive disease, and unevaluable response. No confirmation is required for CR or PR.

All LSP+ subjects who were randomized regardless of whether they have any post-baseline disease progression assessment will be included in the analysis.

10.3.3 Overall Survival in All Subjects

For all subjects, the distribution of OS including median survival time with the corresponding 95% CI will be estimated for each treatment group using Kaplan-Meier methodology and compared between the two randomized treatment groups using the log-rank test, stratified by LSP status (LSP+ versus LSP- versus unknown LSP), ECOG performance status, investigators' preferred platinum therapy, and gender. The hazard ratio and corresponding 95% CI between the two randomized treatment groups in all subjects will also be obtained using the covariate adjusted Cox Proportional Hazard Model with covariates being LSP status (LSP+ versus LSP- versus unknown LSP), ECOG

performance status, investigators' preferred platinum therapy, and gender. In addition, survival rates at Month 12, 18, and 24 will be provided from Kaplan-Meier estimation.

10.3.4 Progression-Free Survival in All Subjects

For all subjects, the distribution of PFS including median PFS time with the corresponding 95% CI will be estimated using Kaplan-Meier methodology and compared between the two randomized treatment groups using the log-rank test, stratified by LSP status (LSP+ versus LSP- versus unknown LSP), ECOG performance status, investigators' preferred platinum therapy, and gender. The hazard ratio and corresponding 95% CI between the two randomized treatment groups will also be obtained using the covariate adjusted Cox Proportional Hazard Model. Covariates to be adjusted are LSP status (LSP+ versus LSP- versus unknown LSP), ECOG performance status, investigators' preferred platinum therapy, and gender. In addition, progression free rates at Month 6, 12, and 18 will be provided from Kaplan-Meier estimation.

10.3.5 Objective Response Rate in All Subjects

The ORR will be estimated and compared between the two randomized treatment groups using covariate adjusted logistic regression with the covariates being by LSP status (LSP+ versus LSP- versus unknown LSP), ECOG performance status, investigators' preferred platinum therapy, and gender. In addition, 95% confidence interval will be constructed for the estimated proportion. All subjects who were randomized regardless of whether they have any post-baseline disease progression assessment will be included in the analysis.

BRR (best response rate) in all subjects will also be summarized for each treatment group, with BRR defined as the best response in all post-treatment disease assessments in the order specified in Section 10.3.2.

10.4 Tertiary Efficacy Analyses

10.4.1 Duration of Overall Response

The duration of overall response (DOR) for a given subject will be defined as the number of days from the day the criteria are met for confirmed CR or PR (whichever is recorded first) to the date that PD is objectively documented by investigators or death, whichever is early. If a subject is still responding on or before the "Cutoff" date, then the subject's data will be censored at date of the last evaluable disease progression assessment on or before the "Cutoff." All events of death occurring on or before the "Cutoff" date will be included for subjects who had not experienced disease progression provided the death occurred within 84 days (12 weeks) of the last disease progression assessment. However, if a disease progression event occurred immediately after that subject missed more than one scheduled consecutive disease progression assessments (e.g., the disease progression event occurred more than 182 days (24 weeks + 14 days) after the last disease progression assessment), this subject will be censored at the last disease progression assessment prior to the disease progression event. For subjects who never experienced CR or PR, the subject's data will not be included.

If the number of subjects with confirmed CR or PR are at least 20% for both randomized treatment groups combined, the distribution of the DOR will be estimated for each treatment group using Kaplan-Meier methodology. Median DOR with the corresponding 95% CI will be provided from Kaplan-Meier estimation. DOR will be summarized for LSP+, LSP-, LSP unknown and all subjects.

10.4.2 Quality of Life

All subjects who do not have baseline measurement or any post-baseline measurements on ITT population will not be included in QoL analyses. Post-baseline measurements will be obtained according to the visit window as in Table 4.

Descriptive statistics will be presented for baseline and each scheduled post-baseline visit (as defined in Table 4) of both overall and domain specific scores of EQ-5D-5L[5] and

NFLSI-17. Mean change (95% CI) from baseline to each scheduled post-baseline visit within treatment group and the mean difference of change (95% CI) from baseline to each scheduled post baseline visit between the two randomized treatment groups will be obtained from the ANCOVA model with treatment group as the factor and baseline value as a covariate.

The mean change from baseline for overall score and domain specific scores at each assessment time point may also be compared between the two randomized treatment groups using a longitudinal repeated measures model. This analysis will include all available data, from baseline to 2 years or disease progression, or initiation of post-treatment therapy, or discontinuation, whichever is latest.

The data will be analyzed at visits with at least 5 subjects for each randomized treatment group. QoL endpoints will be summarized for LSP+, LSP-, LSP unknown and all subjects.

EQ-5D-5L

EQ-5D-5L consists of 5 items: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and a self-rated health visual analogue scale (EQ VAS).

An EQ-5D-5L utility score will be calculated based on country specific preference-weighted index score method. If a country is not included in list of preference weighted index scores, the US preference-weighted index score will be used. If any of the 5 items are missing, the utility score is set to missing. Ambiguous values (e.g., 2 responses are given for a question) is set to missing.

Mean change in utility score (and 95% CI) from baseline to each scheduled post-baseline visit within each treatment group and between the two randomized treatment groups will be obtained from the ANCOVA model with treatment group as the factor and baseline value as a covariate.

Item 6 of EQ-5D-5L, a visual analog scale (VAS) will be analyzed using the same methodology as detailed for the utility score.

NFLSI-17

The overall and domain specific scores will be calculated from the 17 items of NFLSI-17 questioners for each subject based on NFLSI-17 instruction. The items and scales including calculation formula are shown as follows.

Table 7. NCCN-FACT Lung Symptom Index (NFLSI-17)

	Scale	Reverse item?	Item Score
NFLSI-17 Total			
I have a lack of energy	GP1	Yes	4 - Item Response
I have pain	GP4	Yes	4 - Item Response
I am losing weight	C2	Yes	4 - Item Response
I have been short of breath	B1	Yes	4 - Item Response
I feel fatigued	H17	Yes	4 - Item Response
I have been coughing	L2	Yes	4 - Item Response
I have bone pain	BP1	Yes	4 - Item Response
Breathing is easy for me	L4	No	Item Response
I have a good appetite	C6	No	Item Response
I am sleeping well	GF5	No	Item Response
I worry that my condition will get worse	GE6	Yes	4 - Item Response
I have nausea	GP2	Yes	4 - Item Response
I am bothered by hair loss	B5	Yes	4 - Item Response
I am bothered by side effects of treatment	GP5	Yes	4 - Item Response
My thinking is clear	L1	No	Item Response
I am able to enjoy life	GF3	No	Item Response
I am content with the quality of my life right now	GF7	No	Item Response
Subscale			
I have a lack of energy	GP1	Yes	4 - Item Response
I have pain	GP4	Yes	4 - Item Response
I am losing weight	C2	Yes	4 - Item Response
I have been short of breath	B1	Yes	4 - Item Response
I feel fatigued	H17	Yes	4 - Item Response
I have been coughing	L2	Yes	4 - Item Response
I have bone pain	BP1	Yes	4 - Item Response
Breathing is easy for me	L4	No	Item Response
I have a good appetite	C6	No	Item Response
I am sleeping well	GF5	No	Item Response
Disease Related Symptoms-Emotional			
I worry that my condition will get worse	GE6	Yes	4 - Item Response

Table 7. NCCN-FACT Lung Symptom Index (NFLSI-17) (Continued)

	Scale	Reverse item?	Item Score
Subscale (continued)			
Treatment Side Effects			
I have nausea	GP2	Yes	4 - Item Response
I am bothered by hair loss	B5	Yes	4 - Item Response
I am bothered by side effects of treatment	GP5	Yes	4 - Item Response
Function/Well-Being			
My thinking is clear	L1	No	Item Response
I am able to enjoy life	GF3	No	Item Response
I am content with the quality of my life right now	GF7	No	Item Response

NFLSI-17 total score = (Sum individual items sore) × 17/(number of items answered)

NFLSI-Disease Related Symptom-Physical score = (Sum individual items sore for Disease Related Symptom-Physical) × 10/(number of items answered)

NFLSI-Disease Related Symptom-Emotional = Disease Related Symptom Emotional Score

NFLSI-Treatment Side effects score = (Sum individual items sore for Treatment Side Effects) × 3/(number of items answered)

NFLSI-Function/Well-Being score = (Sum individual items sore for function/well-being) × 3/(number of items answered)

If a subject responds 50% or more of the items in a scale (e.g., NFLSI-17 total score), then the raw score of that subject will contribute to the scale. Otherwise, a subject's data will be excluded from the calculation of the summary statistics of that item.

Mean change of each subscale and total scale from baseline to each scheduled post-baseline visit within treatment group and between two randomized treatment groups will

be obtained from the ANCOVA model with treatment group as the factor and baseline value as a covariate.

10.4.3 Performance Status

All subjects who do not have baseline measurement or any post-baseline measurement will not be included in ECOG analyses. ECOG at the scheduled post-baseline visits will be obtained according to the visit window as in Table 4.

Descriptive statistics will be presented for baseline and each scheduled post-baseline visit (as defined in Table 4) of ECOG. Mean change (95% CI) from baseline to each scheduled post-baseline visit within treatment group and the mean difference in change (95% CI) from baseline to each scheduled post-baseline visit between the two randomized treatment groups will be obtained from the ANCOVA model with treatment group as the factor and baseline ECOG as a covariate. The data will be analyzed at visits with at least 5 subjects for each randomized treatment group. ECOG will be summarized for LSP+, LSP-, LSP unknown and all subjects.

10.5 Additional Efficacy Analyses

The following analyses might be performed for the comparison of treatments in LSP-subjects and unknown LSP status subjects, provided there are enough data points in each LSP subgroup.

- For OS and PFS, the log-rank test, stratified by ECOG performance status, investigators' preferred platinum therapy, and gender, will be used to compare the two randomized treatment groups.
- For ORR, the covariate adjusted logistic regression with the covariates being ECOG performance status, investigators' preferred platinum therapy, and gender, will be used to compare between the two randomized treatment groups.
- BRR will also be summarized for each treatment group, with BRR defined as the best response in all post-treatment disease assessments in the order specified in Section 10.3.2.

The following sensitivity analyses for OS will be performed in LSP+, LSP-, LSP unknown and all subjects. The same statistical methods as for the primary and secondary endpoints will be used to compare the two randomized treatment groups.

- Modified OS using all data available in the extracted database without cutoff date.

The following sensitivity analyses for PFS will be performed in LSP+, LSP-, LSP unknown subjects and all subjects.

- Modified PFS using all data available in the extracted database without cutoff date.
- Modified PFS endpoint to consider initiation of post-treatment therapy as an event.

Subgroup analyses for OS defined in Section 10.2, PFS endpoints defined in Section 10.3.1, and ORR defined in Section 10.3.2 will be performed for LSP+, LSP-, LSP unknown and all subjects. The subgroups are

- Gender (male/female)
- Age categories (< 65 years, ≥ 65 years)
- ECOG (0 versus 1)
- Region 1 (Japan, US and western EU and Australia and Canada, Eastern EU/Russia, Other Asia)

Due to the small number of subjects as Black, Asian and others enrolled into this study, no subgroup analysis will be conducted by Race.

The odd ratio of ORR and corresponding 95% CI between two randomized treatment groups by logistic regression model will be estimated for the above subgroups and will be displayed in forest plots. The hazard ratio and 95% CI for OS and PFS will be estimated by the Cox proportional hazards model for the above subgroups and will be displayed in forest plots.

In addition, the following analyses might be performed.

- Depth of response (DpR) (as defined as the number/percentage of subjects achieving 50% of reduction in the best percentage change from baseline in sum of target lesion sizes among confirmed PR for LSP+ and all subjects.
- Analysis of best percentage of change in tumor shrinkage (assessed by largest decrease or smallest increase if no decrease in sum of target lesion sizes from baseline) for LSP+ subjects and all subjects. All post-baseline responses from evaluable tumor assessment will be included (do not need to be confirmed) and will be displayed in waterfall plot.
- The median OS time with the corresponding 95% CI as well as the survival rates at Month 12, 18 and 24 will be provided from Kaplan-Meier estimation for LSP profiled (LSP+ and LSP-), LSP unprofiled (sample provided with indeterminate results or sample not provided) and all subjects.

11.0 Safety Analyses

11.1 General Considerations

Safety analyses will be performed on AST population. Pemetrexed maintenance is NOT considered as study drug. For the visit wise safety analyses, the analysis visit widow as described in Table 4 will be used to align the data.

There will be 5 treatment groups presented in all safety summaries: veliparib 120 mg BID + carboplatin + paclitaxel, each of investigator's choice of platinum doublet therapy group (carboplatin + paclitaxel, cisplatin + pemetrexed, carboplatin + pemetrexed), and overall investigator's choice of platinum doublet therapy group. There will be no statistical comparisons in any of the safety analyses. All safety analysis will be conducted by treatment group for LSP+, LSP-, LSP unknown and all subjects.

11.2 Analyses of Adverse Events

AEs will be coded using the MedDRA coding dictionary. The actual version of the MedDRA coding dictionary will be noted in the CSR.

Analyses of AEs will include only "treatment-emergent" events. "Treatment-emergent adverse events" (TEAEs) are defined as any AEs that first occur on or after the date of first dosing and with an onset date no more than 30 days after the last dose of study drug (veliparib or investigators' choice of standard chemotherapy). TEAEs will be summarized by preferred terms (PT) within a system organ class (SOC). The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC. Subjects reporting more than one AE for a given PT will be counted only once for that term (most severe/highest grade incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one AE within a SOC will be counted only once for that SOC. Subjects reporting more than one AE will be counted only once in the overall total.

The numbers and percentages of subjects experiencing an AE at NCI CTCAE version 4.0 terminology grade,[6] and relationship to veliparib, carboplatin, cisplatin, pemetrexed, or paclitaxel will be provided. SAEs, AEs leading to veliparib, carboplatin, cisplatin, pemetrexed, or paclitaxel discontinuation due to disease progression or not due to disease progression, AEs leading to veliparib dose interruption, cisplatin, pemetrexed, carboplatin, or paclitaxel dose delay, veliparib, carboplatin, cisplatin, pemetrexed, or paclitaxel dose reduction will be summarized by treatment group for LSP+, LSP-, LSP unknown and all subjects.

11.2.1 Analysis of Adverse Events of Special Interest

Analyses of adverse events of special interest will be supported through the summary of MedDRA preferred terms identified using standard MedDRA queries (SMQ-s) and company MedDRA queries (CMQ-s). The incidence rates of these events will be summarized by PT in descending order of veliparib. The same overview summary as for TEAE and listing of subjects' data will be provided for each AESI. All AESI analysis will be conducted by treatment group for LSP+, LSP-, LSP unknown and all subjects unless otherwise specified.

Table 8. Adverse Event of Special Interest in Veliparib Program

Adverse Event of Special Interest	Search Criteria	Event Definition/Medical Concept
Nausea and vomiting	Nausea and vomiting MedDRA preferred terms (PT code 10028813, 10047700)	Treatment-emergent adverse events coded to MedDRA preferred terms.
Seizures	Convulsions SMQ 20000079 (query for convulsions)	Treatment-emergent adverse events coded to MedDRA terms on the broad search list.
Anemia	Haematopoietic erythropenia SMQ 20000029	Treatment-emergent adverse events coded to MedDRA terms on the broad search list.
Thrombocytopenia	Haematopoietic thrombocytopenia SMQ 20000031	Treatment-emergent adverse events coded to MedDRA terms on the broad search list.
Neutropenia	Hematological Toxicity-Neutropenia CMQ 80000154	Treatment-emergent adverse events coded to MedDRA terms.
Infection events within 14 days after neutropenia events	Infections CMQ 80000018 and hematological toxicity-neutropenia CMQ 80000154	Treatment-emergent adverse events from the MedDRA terms on the broad search list.
Haemorrhage events within 14 days after thrombocytopenia	Haemorrhage terms (excl laboratory terms) SMQ 20000039 and hematopoietic thrombocytopenia SMQ 20000031	Treatment-emergent adverse events from the MedDRA terms on the broad search list.
Second/Secondary Malignancies	Secondary Malignancies SMQs, 20000194 and 20000195	Treatment-emergent adverse events from the MedDRA terms on the narrow search list for malignancies are used as a starting point for medical review to search for secondary malignancies.
Myelodysplastic Syndromes (MDS)	Myelodysplastic syndrome SMQ (Narrow) 20000217	Treatment-emergent adverse events from the MedDRA terms on the search list.
Acute Myeloid Leukemia (AML)	Acute myeloid leukaemia PT (10000880)	Treatment-emergent adverse events from the MedDRA preferred terms on the search list.
Changes in reproductive organ function	SMQ 20000210 (fertility disorders)	Treatment-emergent adverse events from the MedDRA terms on the search list.
Teratogenicity		Pregnancies and outcomes will be analyzed individually as they occur.

11.3 Analyses of Deaths

The number of subject deaths will be summarized (1) for deaths occurring within 30 days of the last dose of study drug, (2) for deaths occurring more than 30 days of the last dose of study drug and (3) for all deaths in this study regardless of the number of days relative to the last dose of study drug.

11.4 Analyses of Laboratory and Vital Signs Data

11.4.1 Longitudinal Analyses of Laboratory and Vital Signs Data

Changes from baseline to each scheduled post-baseline visit and Final Visit are analyzed for hematology variables, chemistry variables, urinalysis variables (if collected), and vital signs variables including diastolic/systolic blood pressure, heart rate, and body temperature. Post-baseline visits more than 30 days after the last dose of study drug (veliparib or investigators' choice of standard chemotherapy) will not be included. Subjects who do not have a baseline visit or do not have any post-baseline visits will not be included.

Descriptive statistics will be presented for baseline, each scheduled post-baseline including final visit, and change from baseline.

11.4.2 Analyses of Laboratory Data Using NCI CTCAE v4.0

Following categorization of hematology variables and chemistry variables by NCI CTCAE version 4.0 grades, shift tables from baseline to maximum post-baseline and Final Visit terminology grade will be presented. Post-baseline visits more than 30 days after the last dose of study drug will not be included.

The tables will contain a cross-tabulation of number and percentage of categorized baseline grades versus maximum post-baseline/Final Visit grades. The categories in the cross-tabulation include terminology grades 0 to 4 and missing value. The Grade 0 is defined as the value within the normal range or any value that is outside the normal range but in the opposite direction of toxicity criteria. The maximum post-baseline grade for

each subject is based on the graded values (0 to 4). For each parameter, post-baseline laboratory abnormalities will be summarized by the number and percentage of subjects that have a grade 0 or unknown baseline and also have a grade 1 - 4 post-baseline or worsened from an abnormal baseline value by at least one grade post-baseline. Grade 3 and 4 post-baseline laboratory abnormalities will also be summarized by number and percentage of subjects shifting from grade 0 or unknown to grade 2 at baseline to grade 3 or 4 post-baseline and from grade 3 baseline to grade 4 post-baseline at both the maximum and final observation grade.

Listings of the applicable NCI CTCAE criteria and detailed listings of data for subjects with measurements (regardless of the number of days after the last dose of study drug) meeting the NCI CTCAE grade 3 to grade 4 criteria will be presented.

The definitions of toxicity grades for laboratory parameters are presented in Table 9.

Table 9. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
ALT	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN	Death
AST	> ULN – 3 × ULN	> 3 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN	Death
Alkaline Phosphatase	> ULN – 2.5 × ULN	> 2.5 – 5 × ULN	> 5 – 20 × ULN	> 20 × ULN	Death
Total Bilirubin	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 10 × ULN	> 10 × ULN	Death
Hemoglobin (low)	< LLN – 100 g/L	< 100 – 80 g/L	< 80 g/L	--	Death
Hemoglobin (high)	CH > 0.0 – 20.0 g/L	CH > 20.0 – 40.0 g/L	CH > 40.0 g/L	--	Death
White blood cells	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L	Death
Absolute Neutrophil Count	< LLN – 1.5 × 10^9/L	< 1.5 – 1.0 × 10^9/L	< 1.0 – 0.5 × 10^9/L	< 0.5 × 10^9/L	Death
Platelet count	< LLN – 75.0 × 10^9/L	< 75.0 – 50.0 × 10^9/L	< 50.0 – 25.0 × 10^9/L	< 25.0 × 10^9/L	Death
Glucose (high)	> ULN – 8.9 mmol/L	> 8.9 – 13.9 mmol/L	> 13.9 – 27.8 mmol/L	> 27.8 mmol/L	Death
Glucose (low)	< LLN – 3.0 mmol/L	< 3.0 – 2.2 mmol/L	< 2.2 – 1.7 mmol/L	< 1.7 mmol/L	Death
Creatinine	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 6 × ULN	> 6 × ULN	Death
Uric acid	> ULN – 590 mcmol/L	--	--	> 590 mcmol/L	Death
Inorganic phosphate	< LLN – 2.5 mg/DL	< 2.5 – 2.0 mg/DL	< 2.0 – 1.0 mg/DL	< 1.0 mg/DL	Death
Calcium (low)	< LLN – 2.0 mmol/L	< 2.0 – 1.75 mmol/L	< 1.75 – 1.5 mmol/L	< 1.5 mmol/L	Death
Calcium (high)	> ULN – 2.9 mmol/L	> 2.9 – 3.1 mmol/L	> 3.1 – 3.4 mmol/L	> 3.4 mmol/L	Death
Albumin	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/L	--	Death
Lymphocyte	< LLN – 0.8 × 10^9/L	< 0.8 – 0.5 × 10^9/L	< 0.5 – 0.2 × 10^9/L	< 0.2 × 10^9/L	Death

Table 9. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values (Continued)

Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Sodium (low)	< LLN – 130 mmol/L	--	< 130 – 120 mmol/L	< 120 mmol/L	Death
Sodium (high)	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L	> 160 mmol/L	Death
Potassium (low)	< LLN – 3.0 mmol/L	--	< 3.0 – 2.5 mmol/L	< 2.5 mmol/L	Death
Potassium (high)	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L	> 7.0 mmol/L	Death
Magnesium (low)	< LLN – 0.5 mmol/L	< 0.5 – 0.4 mmol/L	< 0.4 – 0.3 mmol/L	< 0.3 mmol/L	Death
Magnesium (high)	> ULN – 1.23 mmol/L	--	> 1.23 – 3.30 mmol/L	> 3.30 mmol/L	Death
Bicarbonate	< LLN – 16 mmol/L	< 16 – 11 mmol/L	< 11 – 8 mmol/L	< 8 mmol/L	Death

11.4.3 Drug-Induced Liver Injury

Elevations relative to the upper limit of normal (ULN) in alanine transaminase (ALT), AST, total bilirubin, and alkaline phosphatase as outlined in the FDA Guidance for Industry pertaining to premarketing clinical evaluations for drug-induced liver injury (DILI) will be summarized using the maximum post-baseline values:

- ALT: > 3 × –, > 5 × –, > 10 × –, or > 20 × ULN
- AST: > 3 × –, > 5 × –, > 10 × –, or > 20 × ULN
- Total bilirubin > 2 × ULN
- Alkaline phosphatase > 1.5 × ULN
- ALT or AST (> 3 × ULN) accompanied by total bilirubin (> 2 × ULN) at the same visit (potential Hy's Law criteria3)

Plots will be generated for total bilirubin vs. ALT values and total bilirubin vs. AST values in the eDISH format. For each subject, the visit with the maximum total bilirubin value relative to the ULN, then the maximum ALT (or AST) value relative to the ULN

will be used in the plot. A listing of lab data for subjects meeting potential Hy's law criteria will be provided.

11.5 Analyses of Safety by Subgroup (All population)

11.5.1 Adverse Events Subgroup Analyses

Subgroup analyses may be performed on treatment-emergent G3/4 AEs for imbalance safety observation between randomized treatment groups. The subgroups to be evaluated include:

- Gender (male/female)
- Age categories (< 65 years, ≥ 65 years)
- Region 2 (Japan, US, EU/Canada)

Due to the small number of subjects as Black, Asian and others enrolled into this study, no subgroup analysis will be conducted by Race.

11.5.2 Laboratory Variables Subgroup Analyses

Subgroup analyses for all subjects will be performed for the shifts from baseline 0 - 2 to maximum grade of 3 and 4 the hematology variables and chemistry variables for the following subgroups:

- Gender (male/female)
- Age categories (< 65 years, ≥ 65 years)
- Region 2 (Japan, US, EU/Canada)

Due to the small number of subjects as Black, Asian and others enrolled into this study, no subgroup analysis will be conducted by Race.

12.0 Summary of Changes

12.1 Summary of Major Changes from the Last Version of the SAP

1. Clarified the definition of LSP subgroups including the LSP+ primary population.

   Rational: Patients with analytically valid LSP results can be included in the LSP+ subgroups (primary analysis set) regardless of RNA mass (including those below the 35 ng RNA threshold described in the assay protocol) or re-test status.

   - Although the likelihood of QC failure increases with the decreased RNA mass, the LSP subgroup determination (positive or negative) remains reliable among QC-pass samples.
   - The LSA testing protocol allows re-testing to resolve trouble-shooting (QC failure or qPCR failure) with no upper limit to the number of repeat runs.
   - The assay data transfer specifications have been revised to include subcategories that will capture data related to multiple runs

2. Added reference for median OS for sample size calculation to address FDA's comment

   Rational: To address FDA comment received on Jan 2019: "In the SAP, please provide the assumed medians for the final OS analyses in the LSP-positive and ITT populations."

3. Added summary for LSP results in the patient disposition section

13.0 References

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