1.0 Title Page

Statistical Analysis Plan

Study M14-217

Randomized, Blinded, Multicenter, Phase 2 Study Comparing Veliparib Plus FOLFIRI ± Bevacizumab Versus Placebo Plus FOLFIRI ± Bevacizumab in Previously Untreated Metastatic Colorectal Cancer

Date: 23 February 2017

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3.0 Introduction

This statistical analysis plan (SAP) describes the full statistical analyses for veliparib (ABT-888) Protocol M14-217 dated 16 July 2015. It will provide details of statistical methods and describe analysis conventions to guide the statistical programming work.

Unless noted otherwise, all analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

Primary Objective:

The primary objective of the study is to assess whether the addition of oral veliparib to FOLFIRI will improve progression-free survival (PFS) in subjects with previously untreated metastatic colorectal cancer (mCRC).

Secondary Objectives:

The secondary objectives of the study are to assess overall survival (OS), objective response rate (ORR), safety, and tolerability.

Tertiary Objectives:

The tertiary objectives are to assess duration of response (DOR) and the effects on a patient's Eastern Cooperative Oncology Group (ECOG) performance status.

4.2 Design Diagram

This is a randomized, blinded, Phase 2 multicenter study evaluating the efficacy and tolerability of veliparib plus FOLFIRI versus placebo plus FOLFIRI in subjects with previously untreated metastatic colorectal cancer. At the discretion of the Investigator, subjects can also be treated with bevacizumab.

The study was designed to enroll approximately 120 subjects at approximately 60 study sites. Subjects will be stratified by the planned use of bevacizumab (planned bevacizumab use versus no planned use with bevacizumab) and regions of the world (North America versus rest of world). Within each stratification group, subjects will be randomized in a 1:1 ratio to one of two protocol therapy groups as follows:

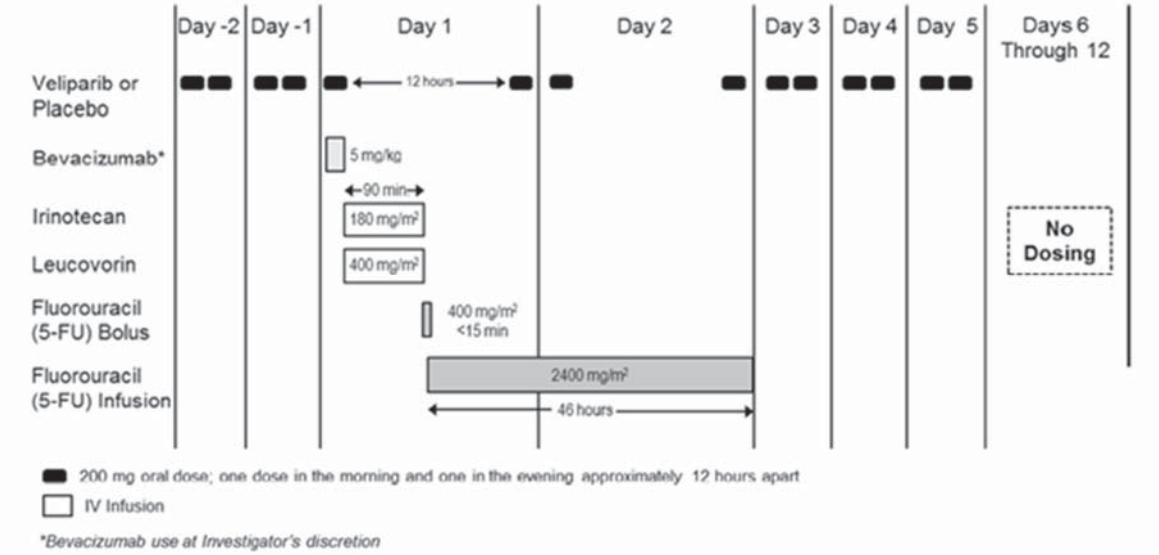
a. Veliparib plus FOLFIRI ± bevacizumab
b. Placebo plus FOLFIRI ± bevacizumab

Enrollment will be gated to ensure that at least 60 subjects are enrolled in both the "planned bevacizumab use" group and "no planned bevacizumab use" group for a total of ~120 subjects.

Dosing Schedule Overview

One cycle of protocol therapy consists of 14 days, defined as Day –2 through Day 12. Dosing of oral veliparib/placebo will begin 2 days prior to the start of FOLFIRI and will continue twice a day (BID) for a total of 7 consecutive days. At the discretion of the Investigator, bevacizumab (5 mg/kg) may be administered intravenously immediately preceding FOLFIRI. FOLFIRI (irinotecan, leucovorin, 5-FU bolus (saline bolus for subjects randomized to the veliparib arm), 5-FU) will be administered starting on Day 1 of each 14-day cycle. FOLFIRI is only to be given after veliparib/placebo dosing on cycle Day –2 and Day –1 are confirmed. An overview of the protocol schedule constituting one treatment cycle is shown in Figure 1. Additional details regarding dosing with veliparib/placebo, FOLFIRI and bevacizumab can be found in Section 5.5 of the Protocol.

Figure 1. Protocol Therapy Dosing Schedule Overview



Visit Schedule Overview

Screening procedures and baseline radiographic tumor assessments will be performed within 28 days prior to the first dose of veliparib/placebo on Cycle 1 Day –2 (C1D–2). Study visits will be conducted on Day 1 and Day 8 of the first and second cycle, then on Day 1 of each subsequent cycle. Subjects will continue protocol therapy and attending study visits until they meet one of the defined discontinuation criteria found in Section 5.4 of the Protocol. When the Investigator has determined that a subject meets the criteria for discontinuation, a Final Visit will be conducted. All subjects will have one Follow-Up Visit approximately 30 days after the last dose of protocol therapy. Sites will begin collecting post-treatment and survival information 4 weeks after the Final Visit.

Post-baseline radiographic tumor assessment will be conducted every 8 weeks from C1D1 (prior to the start of a new cycle) until radiographic progression. Radiographic tumor assessments will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1.

4.3 Sample Size

A minimum of 70 PFS events was chosen to provide adequate precision in the hazard ratio estimate. Assuming median PFS times of 9.4 months in the FOLFIRI ± bevacizumab arm and 15.7 months in the veliparib plus FOLFIRI ± bevacizumab arm, based on a minimum of 70 PFS events, the expected 95% confidence interval for the estimated hazard ratio would be approximately 0.37 to 0.96. A total of 120 subjects will be enrolled into the study. Assuming a total enrollment period of 12 months, it is anticipated that the study will complete by end of the 22nd month if the true median times for each treatment arm are as assumed above.

4.4 Interim Analysis

To ensure subject safety and assess the efficacy of veliparib during the study, AbbVie performed one efficacy/futility analysis and two safety interim analyses. An Internal Monitoring Committee (IMC) was formed to review the interim data and make recommendations to the study team regarding the conduct of the study. A separate IMC agreement defines the roles and responsibilities of the IMC, including its membership, scope, timing of meetings, and communication plan.

The first safety interim was planned to occur at least 8 – 10 weeks after 20 subjects in the "planned bevacizumab use" group are randomized. A second interim analysis for both efficacy and safety was planned to be conducted at least 8 – 10 weeks after 35 PFS events have occurred.

The first IMC meeting reviewed safety data on August 31, 2015, and the second IMC meeting reviewed safety and efficacy data on May 16, 2016. The IMC recommended continuing the study after both of the IMC meetings.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Two study populations will be analyzed, defined as follows:

- Intent-To-Treat (ITT) population – all subjects who were 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 were randomized by IRT and took at least 1 dose of study drug (veliparib/placebo). The data from AST population will be analyzed by the actual treatment that subject received.

5.2 Variables Used for Stratification of Randomization

Subject randomization will be stratified by Region (North America vs. Rest of World) and Planned Bevacizumab Use (Planned Bevacizumab Use vs. No Planned Bevacizumab Use) into 4 strata as follows:

Group	Strat Factor 1	Strat Factor 2
1	North America	Planned Bevacizumab Use
2	North America	No Planned Bevacizumab Use
3	Rest of World	Planned Bevacizumab Use
4	Rest of World	No Planned Bevacizumab Use

During randomization, subjects within each of the 4 strata were randomized in a 1:1 ratio to either the veliparib plus FOLFIRI group or the placebo plus FOLFIRI group.

6.0 Analysis Conventions

General Considerations

Due to the proof-of-concept nature of the study, all of the analyses will be conducted in an estimation fashion. Ninety-five percent confidence intervals will be presented and *P*-values will be not provided. The date of randomization is defined as the date that the IRT issues a randomization number.

All randomized subjects will be included in the efficacy analyses. All subjects who receive at least one dose of the study drug (veliparib/placebo) will be included in the safety analysis.

Definition of Study Drug

Unless otherwise specified, the study drug in this document refers to veliparib/placebo.

Definition of Study Therapy

Unless otherwise specified, the study therapy in this document refers to all protocol allowed therapies including veliparib/placebo, bevacizumab, ironotecan, leucovorin, and 5-FU infusion/saline bolus.

Stratification Factor for Efficacy Analyses

Planned bevacizumab use (planned bevacizumab use versus no planned bevacizumab use) will be used in all stratified analyses of the efficacy endpoints. The stratification factor value under which the subject is randomized by the IRT will be used in the efficacy analyses.

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 for the shift analysis of lab parameters; the arithmetic average will be calculated and used as the value for that day for the change from baseline in performance status (ECOG), laboratory, and vital signs parameters.

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 for treated subjects (or the date of randomization for non-treated subjects).

Dealing with Surgical Intervention

As a result of treatment, subjects may suspend protocol therapy to undergo surgical resection with curative intent for metastatic disease. Subjects may then restart protocol therapy beginning with the next scheduled cycle provided they have recovered from surgery. With respect to tumor measurements, the first post-surgery radiographic assessment will serve as the new post-surgery baseline. Target or non-target lesions existing before and remaining after surgery should continue to be evaluated using RECIST, Version 1.1. Details regarding tumor response measurements can be found in Protocol Appendix D.

Definition of Final Visit

For ECOG, laboratory and vital signs variables, Final Visit is defined as the last non-missing observation collected within 30 days following the last dose of study drug (veliparib/placebo). All post-baseline assessments collected more than 30 days after the last dose of study drug (veliparib/placebo) will not be included in the analyses of laboratory and vital signs variables.

Definition of Cycle X Rx Day

Cycle X Rx Day 1 for each cycle during the treatment period (1 cycle is defined as a minimum of 14 days) is defined as 2 days prior to the first dose day of Fluorouracil Infusion in each cycle. Cycle X Rx Day is defined as days relative to Cycle X Rx Day 1 of each cycle. Cycle X Rx Day is a negative (positive) value when the time point of interest is prior to (after) Cycle X Rx Day 1. The day before Cycle X Rx Day 1 is therefore Cycle X Rx Day –1 and there is no Cycle X Rx Day 0. After treatment of veliparib/placebo is over, nominal Cycle X Rx Day 1 is generated as 14 days from the last Cycle X Rx Day 1.

Definition of Analysis Windows

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

For visit-wise longitudinal analyses such as change from baseline to all post-baseline assessments in ECOG, laboratory, and vital signs values, the time windows specified in Table 1 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 X Rx Day for each scheduled visit.
- Determine the window around a specific nominal Cycle X Rx Day as in Table 1.
- 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.

The data will only be analyzed for visits that have at least 5 subjects' observation for either of treatment group.

Table 1. Time Windows for Visit-Wise Analysis (ECOG, Laboratory, and Vital Signs)

Protocol Defined Study Visit	Cycle X Rx Day	Nominal Cycle Rx Rx Day**	Time Window (Cycle X Rx Day Range)*	Time Window (Cycle X Rx Day Range)***
Cycle 1 Day –2	Cycle 1 Rx Day 1	Baseline	Baseline	Baseline
Cycle 1 Day 1	Cycle 1 Rx Day 3	3	[2, 6]	[2, 9]
Cycle 1 Day 8*	Cycle 1 Rx Day 10	10	[7, 13]	
Cycle 2 Day 1	Cycle 2 Rx Day 3	3	[–1, 6]	[–5, 9]
Cycle 2 Day 8*	Cycle 2 Rx Day 10	10	[7, 13]	
Cycle 3 Day 1	Cycle 3 Rx Day 3	3	[–1, 9]	[–5 ,9]
Cycle X Day 1	Cycle X Rx Day 3	3	[–5, 9]	[–5, 9]
Final Visit	Final Visit	See Final Visit	See Final Visit	See Final Visit

* For Chemistry, Hematology and Urinalysis only.

** For ECOG, nominal Cycle Rx Day 1 will be generated as 14 days from Day 1 of the last cycle after treatment is over.

*** For ECOG and Vital Signs.

7.0 Demographics, Baseline Characteristics, Medical History, Previous/Concomitant Medications and Prior Oncology Therapies

The ITT population will be used in the analyses of demographic, baseline characteristics, medical history, and previous/concomitant medication and prior oncology therapies. For the safety interims, all analyses will also be performed on the ITT population subset for planned bevacizumab use.

7.1 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Country
- Geographical Region [North America, Rest of World]
- Planned Bevacizumab Use (as randomized) [planned bevacizumab use, not planned bevacizumab use]

- Bevacizumab Use (actual) [bevacizumab received, bevacizumab not received]
- Race
- Gender
- Age (continuous and by categories [< 65 versus ≥ 65])
- Height
- Weight
- Smoking history (current smoker versus never smoked versus past smoker)
- ECOG

The number of subjects with missing information will also be summarized.

Categorical data will be summarized by numbers and percentages in each category. Continuous data will be summarized by mean, standard deviation, median, minimum and maximum values.

The Fisher's exact test will be used for testing homogeneity between the two treatment groups for the categorical demographic and baseline characteristics data. The missing information of categorical data will not be included in the test. An ANOVA model with treatment group as the factor will be used for testing homogeneity between the two treatment groups for the continuous demographic and baseline characteristics data.

7.2 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment group. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system. There will be no statistical comparison for the medical history between the two treatment groups.

7.3 Prior and Concomitant Medications and Prior Oncology Therapies

The number and percentage of subjects who took at least one dose of medication other than study drug will be summarized by the generic name coded by WHO dictionary. This analysis will be performed for prior and concomitant medications separately. The number and percentage of subjects who have prior oncology therapies will be summarized by regimen names. There will be no statistical comparison for the prior and concomitant medications and prior oncology therapies between the two treatment groups.

8.0 Subjects Disposition

Analyses for the subject disposition will be performed on the ITT population.

The screen failure reasons will be summarized for the screen failure subjects. The number of randomized subjects and the number of treated subjects will be summarized by country and investigator for each treatment group respectively.

The number and percentage of subjects who discontinue study and all study treatment (all protocol therapy) will be summarized for each treatment group. All reasons and primary reason (per eCRF) for discontinuation of study and each treatment (veliparib/placebo, bevacizumab, irinotecan, leucovorin, fluorouracil bolus or fluorouracil infusion) given by each subject will be included in the summary. There will be no statistical comparison for the subject disposition.

9.0 Study Therapy Exposure and Compliance

9.1 Exposure to Study Therapy

Analyses for the study therapy exposure will be performed on the AST population. The number of cycles that subjects are exposed to veliparib/placebo, bevacizumab, irinotecan, leucovorin, and 5-FU infusion/saline bolus will be summarized.

In addition, the following will be summarized for veliparib/placebo:

Duration of study drug exposure is defined as the total number of days a subject received study drug.

Average dosed days per cycle of study drug is defined as the total number of days a subject received study drug divided by the number of cycles that the subject is exposed to study drug.

Descriptive statistics (mean, standard deviation, median, and range) will be used to summarize duration and average dosed days per cycle of study drug. An ANOVA model will be used for the comparisons of duration and average dosed days per cycle of exposure between the two treatment groups. In addition, the number and percentage of subjects exposed to study drug will be summarized for each of the following 35-day duration intervals.

- 1 to 35 days
- 36 to 70 days
- 71 to 105 days
- 106 to 140 days
- 141 to 175 days
- 176 to 210 days
- 211 to 245 days
- > 245 days

9.1.1 Dose Reductions, Interruptions and Delays

The numbers and percentages of subjects having dose reductions, interruptions, or delays will be summarized for each treatment group.

Dose Reductions

If a subject has any dose reduction from the previous dose of veliparib/placebo, Irinotecan, or 5-FU Infusion, this subject will be considered as having experienced a dose

reduction of the respective drug. Dose reductions of Leucovorin, bevacizumab and the 5-FU/Saline Bolus are not allowed.

Dose Interruptions

Dose interruptions are defined for veliparib/placebo only, and are considered within each cycle. Each instance that a subject skips one or more consecutive days of dosing will be counted as a single dose interruption. Multiple instances of skipped dosing days are counted as multiple dose interruptions. Alternatively, a subject will be considered as having a dose interruption if the subject does not achieve the required 7 days of dosing without skipping any consecutive days.

Dose Delays

If the difference between dose dates of two consecutive doses of veliparib/placebo, Irinotecan, 5-FU infusion or 5-FU bolus, or bevacizumab, is more than 21 days, the subject will be considered as having experienced a dose delay.

9.2 Compliance

Analyses for the compliance of study drug will be performed on the AST population. Unless otherwise directed by the Investigator, the subject will be considered compliant with all study therapy if at least 80% of the assigned dose of veliparib/placebo is taken during a cycle. The number and percentage of subjects will be summarized by treatment group for (1) at least 80% compliant based on investigator opinion for every cycle, (2) at least 80% compliant based on investigator opinion for all but one cycle, (3) less than 80% compliant based on investigator opinion for more than one cycle. There will be no statistical comparison for this analysis.

In addition, the compliance based on investigator opinion for each subject during the whole course of study will be provided in the listing.

10.0 Efficacy Analysis

10.1 General Considerations

Due to the proof-of-concept nature of the study, all of the analyses will be conducted in an estimation fashion. Ninety-five percent confidence intervals will be presented and *P*-values will be not provided.

Efficacy analyses will be performed on ITT population. The date of randomization is defined as the date when the randomization number is issued by IRT.

The 'Event Cutoff' date for the PFS, DOR, and OS endpoints is December 31, 2016, defined by the data cleaning cutoff for the database lock after 70 events of disease progression or death have occurred in both treatment arms combined. It is the censoring date for both the PFS, DOR and OS endpoints for the subjects who have not had an event prior to that day.

Statistical analyses will be performed using SAS version 9.4 under the UNIX operating system.

10.2 Primary Efficacy Analysis

The primary efficacy analysis will be a comparison of progression-free survival (PFS) between the two treatment groups.

For a given subject, PFS will be defined as the number of days from the date the subject was randomized to the first date the subject experiences an event of disease progression (as determined by the investigator) or to the date of death (all causes of mortality) if disease progression is not reached. All events of disease progression (as determined by investigators) occurring on or before the "Event Cutoff" date will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. However, if a disease progression event occurred immediately after that subject missed two or more scheduled consecutive disease progression assessments (e.g., the disease progression event occurred more than 112 days

after the last evaluable disease progression assessment), the subject will be censored at the last radiographic disease progression assessment prior to the disease progression event. All events of death occurring on or before the "Event Cutoff" date will be included for subjects who had not experienced disease progression provided the death occurred within 8 weeks of the last evaluable disease progression assessment. For those subjects who take other non-protocol anti-cancer therapies after discontinuation of the study drug prior to disease progression, the primary efficacy endpoint of PFS will be censored at the date of subject's initiation of other anti-cancer therapies. If the subject does not have an event of disease progression nor has the subject died as described above, the subject's data will be censored at the date of the subject's last evaluable radiographic disease progression 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.

The distribution of PFS will be estimated for each treatment group using Kaplan-Meier methodology. Median PFS time will be estimated and 95% confidence interval for the estimated median PFS time will be presented for each treatment group. The Cox Proportional Hazard Model will be used to estimate the hazard ratio and 95% confidence interval comparing the two treatment groups, stratified by planned bevacizumab use (planned use versus no planned use).

10.3 Secondary Efficacy Analyses

Secondary efficacy analyses comparing the effects of veliparib plus FOLFIRI and placebo plus FOLFIRI on the following set of endpoints will be performed: overall survival (OS) and objective response rate (ORR).

10.3.1 Overall Survival

Time to death (overall survival) for a given subject will be defined as the number of days from the date that the subject was randomized to the date of the subject's death. All events of death 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 "Event Cutoff" date, the data will be censored at the date when the subject was last known to be alive (survival follow-up and study visit, etc.).

The distribution of OS will be estimated for each treatment group using Kaplan-Meier methodology. Median survival time will be estimated and 95% confidence interval for the estimated median survival time will be presented for each treatment group. The Cox Proportional Hazard Model will be used to estimate the hazard ratio and 95% confidence interval comparing the two treatment groups, stratified by planned bevacizumab use (planned use versus no planned use).

10.3.2 Objective Response Rate

Objective response rate (ORR) is defined as the proportion of subjects with complete response (CR) or partial response (PR) per RECIST (version 1.1). For subjects who underwent surgery, ORR is not evaluated after surgery.

The ORR will be estimated within each group and 95% confidence intervals will be constructed based on the exact binomial distribution. The Mantel-Haenszel method will be used to calculate the difference in proportions between the two groups, stratified by planned bevacizumab use (planned use versus no planned use), along with the 95% confidence interval of the difference. All subjects who were randomized regardless of whether they have any post-baseline disease progression assessment will be included in the analysis.

10.4 Tertiary Efficacy Analyses

Tertiary efficacy analyses comparing the effects of veliparib plus FOLFIRI and placebo plus FOLFIRI on the following set of endpoints will be performed: duration of overall response (DOR) and changes in ECOG performance status.

10.4.1 Duration of Overall Response

The duration of overall response for a given subject will be defined as the number of days from the day the criteria are met for CR or PR (whichever is recorded first) to the date that

PD is objectively documented by investigators. If a subject is still responding on or before the "Event Cutoff" date then the subject's data will be censored at date of the last available disease progression assessment on or before the "Event Cutoff." For subjects who never experienced CR or PR, the subject's data will not be included.

If the ORR is at least 30% for both treatment groups combined, the distribution of the duration of overall response will be estimated for each treatment group using Kaplan-Meier methodology. Median duration of overall response with the corresponding 95% CI will be provided from Kaplan-Meier estimation for each treatment group. The Cox Proportional Hazard Model will be used to estimate the hazard ratio and 95% confidence interval comparing the two treatment groups, stratified by planned bevacizumab use (planned use versus no planned use). If the ORR is not at least 30% for both treatment groups combined, only the Kaplan-Meier estimates will be summarized in a descriptive fashion.

10.4.2 ECOG Performance Status

ECOG performance status is a scale from 0 to 4 collected at baseline, Day 1 of each cycle and final visit. All subjects who do not have baseline measurement or any post-baseline measurements 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 1. Descriptive statistics will be presented for baseline and each scheduled post-baseline visit (as defined in Table 1) of ECOG by treatment group. Mean change (95% CI) from baseline to each scheduled post-baseline visit within each treatment group and the mean difference in change (95% CI) from baseline to each scheduled post-baseline visit between the two treatment groups will be obtained from the ANCOVA model with treatment group as the factor and baseline ECOG as a covariate.

10.5 Additional Efficacy Analyses

In addition to the stratified log-rank test for the primary and secondary efficacy endpoints, the following analyses may be performed for the comparison of PFS, OS, and ORR between the two treatment groups.

- Un-stratified log-rank test and the Cox proportional hazards model for PFS, OS.
- Modified PFS endpoint to examine sensitivity to different censoring methods, described in detail below.
- Modified efficacy endpoint OS to censor at the date of subject's initiation of other post anti-cancer therapies.
- Subgroup analysis by smoking history, gender, region, baseline ECOG, etc.

Sensitivity Analysis for PFS Endpoint

In addition to the Primary PFS analysis, modified PFS analyses will be performed to examine the sensitivity to various censoring methods. A summary of these are in the following table.

	Name for Analysis					
Type of Censoring	**Primary**	**Mod1**	**Mod2**	**Mod3**	**Mod4**	**Mod5**
First Post-Treatment Anti-Cancer Therapy	Yes	No	Yes	Yes	Yes	No
56 day death window	Yes	Yes	No	Yes	Yes	No
Blind Break	No	No	No	Yes	No	No
Missing Scans	Yes	No	No	No	No	No

Yes means censor; No means do not censor.

Apply this to censor PFS and DOR; ORR will be evaluated only up to the censoring time defined by the above censoring rules.

Note that ORR and DoR are also impacted by surgery.

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will be performed on AST population, as well as on the AST population with actual bevacizumab use. For the visit wise safety analyses, the analysis visit widow as described in Table 1 will be used to align the data. Only P values ≤ 0.100 when rounded to three digits will be presented.

11.2 Analysis of Adverse Events

Analyses of adverse events will include only "treatment-emergent" events. "Treatment-emergent adverse events" are defined as any adverse events that first occur on or after the date of first dosing with veliparib/placebo and with an onset date no more than 30 days after the last dose of veliparib/placebo. Treatment-emergent adverse events will be summarized by preferred terms (PTs) within a System and Organ Class (SOCs) according to the version of the MedDRA adverse event coding dictionary at the time of the database lock. The SOCs will be presented in alphabetical order and the PTs will be presented in alphabetical order within each SOC.

Comparisons of the rates of subjects experiencing an adverse event between the two treatment groups will be performed using Fisher's exact test, as applicable.

Adverse Event Overview

An overview of adverse events will be presented for each treatment arm consisting of the number and percentage of subjects experiencing at least one event for the following adverse event categories:

- Any treatment-emergent adverse event
- Any treatment-emergent adverse event that is rated by the investigator as a reasonable possibility of being related to each of: veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab
- Any treatment-emergent NCI terminology grade 3, grade 4, or grade 5 adverse event
- Any treatment-emergent NCI terminology grade 3 or grade 4
- Any treatment-emergent serious adverse event
- Any treatment-emergent adverse event leading to discontinuation of each of: veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab

- Any treatment-emergent adverse event leading to discontinuation of each of: veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab due to disease progression
- Any treatment-emergent adverse event leading to discontinuation of each of: veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab not due to disease progression
- Any treatment-emergent adverse event leading to interruption of each of: veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab
- Any treatment-emergent adverse event leading to dose reduction of each of: veliparib, irinotecan, and fluorouracil (5-FU) infusion
- Any treatment-emergent adverse event of special interest
- Any treatment-emergent adverse event leading to death
- All deaths.

Adverse Event by SOC and PT

In addition to the AE categories listed under Adverse Event Overview, the numbers and percentages of subjects experiencing treatment-emergent adverse events will be summarized by treatment group for the following adverse event categories:

- Any treatment-emergent adverse event with number broken down by maximum NCI terminology grade
- Any treatment-emergent adverse event with number broken down by maximum relationship to each of: veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab.
- Any treatment-emergent adverse event that is rated by the investigator as a reasonable possibility of being related to each of: veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab, by the investigator (Reasonable Possibility Related) with NCI terminology grade 3, grade 4, or grade 5 adverse event
- Any treatment-emergent adverse event that is rated by the investigator as a reasonable possibility of being related to each of: veliparib, irinotecan,

fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab by the investigator (Reasonable Possibility Related) with NCI terminology grade 3 or grade 4 adverse event

- Any treatment-emergent serious adverse event with number broken down by maximum NCI terminology grade
- Any treatment-emergent serious adverse event with number broken down by maximum relationship to veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab.
- Any treatment-emergent serious adverse event that is rated by the investigator as a reasonable possibility of being related to each of veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab, by the investigator (Reasonable Possibility Related)
- Any treatment-emergent NCI terminology grade 3, grade 4, or grade 5 serious adverse event
- Any treatment-emergent adverse event that is rated by the investigator as a reasonable possibility of being related to each of veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab by the investigator (Reasonable Possibility Related) with NCI terminology grade 3, grade 4, or grade 5 serious adverse event
- Any treatment-emergent NCI terminology grade 3 or grade 4 serious adverse event
- Any treatment-emergent adverse event that is rated by the investigator as a reasonable possibility of being related to each of veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, and bevacizumab by the investigator (Reasonable Possibility Related) with NCI terminology grade 3 or grade 4 serious adverse event
- Any treatment-emergent adverse event leading to interruption of veliparib, irinotecan, fluorouracil (5-FU) infusion, fluorouracil (5-FU) bolus, or bevacizumab
- Any treatment-emergent adverse event leading to dose reduction of veliparib, irinotecan, or 5-FU infusion

- Any treatment-emergent adverse event leading to death that is rated by the investigator as a reasonable possibility of being related to veliparib by the investigator (Reasonable Possibility Related)

For all adverse event summaries, the number and percentage of subjects experiencing treatment-emergent adverse events will be tabulated according to SOC and PT for each treatment arm. Subjects reporting more than one AE for a given PT will only be counted once for that term. Subjects reporting more than one adverse event within an SOC will only be counted once for that SOC. Subjects reporting more than one AE will only be counted once in the overall total.

Adverse Event by Frequency

The number and percentage of subjects experiencing treatment-emergent adverse events and treatment-emergent serious adverse events will be tabulated according to preferred term and sorted by overall frequency. Percentages will be compared within the two pair-wise comparisons using Fisher's exact tests. Only P values ≤ 0.100 when rounded to three digits will be presented.

Adverse Event of Special Interest

Treatment-emergent AEs and serious AEs of special interest based on SMQ or PMQ broad searches may be summarized.

11.3 Deaths

The number of subject deaths will be summarized (1) for deaths occurring while the subject was still receiving study drug in this study, (2) for deaths occurring off treatment within 30 days after the last dose of study drug, and (3) for all deaths in this study regardless of the number of days after the last dose of study drug. Listings of deaths occurring within 30 days after the last dose of study drug, and deaths occurring after 30 days after the last dose of study drug will be provided. There will be no statistical comparison for above analyses.

11.4 Analysis of Laboratory and Vital Signs Data

Longitudinal Analyses of Laboratory and Vital Signs Data

Changes from baseline are analyzed for each scheduled post-baseline visit and Final Visit (defined as in Table 1) for hematology variables, chemistry variables, 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 will not be included. Subjects that do not have a baseline visit or do not have any post-baseline visits will not be included. The data will be analyzed at visits with at least 5 subjects overall for each treatment group.

Descriptive statistics will be presented for baseline, each scheduled post-baseline, and Final Visit by each treatment group. The comparison between the two treatment groups in mean change from baseline to each scheduled post-baseline visit and to Final Visit will be performed using the ANOVA model with treatment group as the factor.

Analyses of Laboratory Data Using NCI CTCAE

Following categorization of laboratory variable values by NCI CTCAE version 4.0 grades, shift tables from baseline to maximum post-baseline and Final Visit terminology grade will be assessed. 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. All treated subjects will be included in the cross tabulation regardless whether baseline or post baseline measurements are collected.

The number and percentage of subjects experiencing a shift from a baseline terminology grade of 0 to grade 2 to a maximum post-baseline grade of 3 to grade 4, and from a baseline grade of 0 to grade 2 to a Final Visit grade of 3 to grade 4 will be summarized and compared between the two treatment groups using Fisher's exact test. All treated

subjects with baseline terminology grade of 0 to grade 2 and post baseline grades will be included in this analysis.

Listings of the applicable NCI CTC 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 CTC grade 3 to grade 4 criteria will be presented.

11.5 Analyses of Vital Signs Using Criteria for Potentially Clinically Significant Vital Sign Values

Vital signs values will be assessed for potential clinical significance through the application of criteria developed at AbbVie as detailed in the table below.

Systolic Blood Pressure	> 150 mmHg and > 20 mmHg higher than baseline
	< 70 mmHg and a decrease of ≥ 30 mmHg from baseline
Diastolic Blood Pressure	> 100 mmHg and higher than baseline
	< 50 mmHg and a decrease of ≥ 20 mmHg from baseline
Pulse Rate	> 120 bpm and an increase of ≥ 30 bpm from baseline
	< 50 bpm and a decrease of ≥ 30 bpm from baseline
Temperature	≥ 38.9°C
	≤ 35.6°C

The number and percentage of subjects with post baseline values meeting Criteria for Potentially Clinically Significant Vital Signs values will be summarized. A subject who has at least one post-baseline measurement will be included in the summary. If a subject does not have any vital sign measurements at baseline, but has a post-baseline measurement which meets the above criteria for blood pressure and pulse rate, this subject is considered as meeting the potentially clinically significant vital signs values for the measurement. If a subject has both baseline and post-baseline measurements, the post-baseline value must also be more extreme than the baseline values for blood pressures and pulse rates. A separate listing will be provided that presents all of the subjects and values meeting the criteria. The comparisons of the rates of subjects meeting the above criteria between the two treatment groups will be performed using Fisher's exact test.

Document Approval

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