Protocol MDV3800-13 (C3441010)

A Single-Arm, Open-Label, Multicenter, Extended Treatment, Safety Study in Patients Treated With Talazoparib

Statistical Analysis Plan

Version: Final 1.0

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study MDV3800-13 (C3441010) is based on the Protocol Amendment 1 dated 29JUL2016.

Table 1 Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
Final 1.0		

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study PF-06944076, MDV3800-13 (C3441010).

The data will be analyzed by Medivation (a wholly owned subsidiary of Pfizer Inc.).

All analyses stated in this Statistical Analysis Plan will be performed using SAS® software version 9.4 or later.

2.1. Study Objective

- To obtain additional safety data on long-term talazoparib use.

2.2. Study Design

This is a single-arm, open-label, extended treatment, safety study in patients treated with talazoparib (also known as MDV3800, BMN 673) as a single agent or in combination with another agent in qualifying originating clinical studies sponsored by Medivation. The safety and tolerability of long-term talazoparib use will be evaluated, and the data collected will be limited to safety assessments. The study provides access to single-agent talazoparib for qualifying patients who may benefit from continuing therapy with talazoparib.

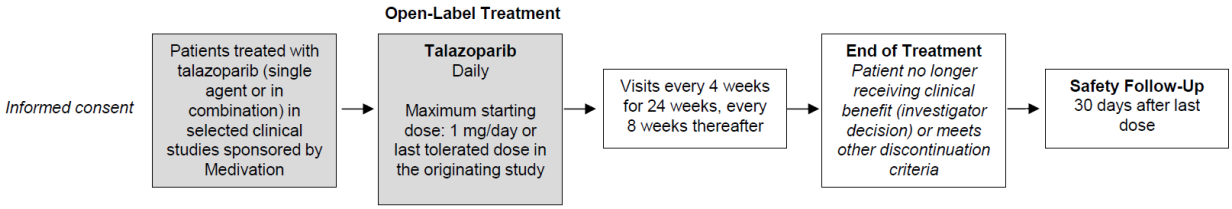
Eligible patients must have received talazoparib in a qualifying study and have no ongoing grade 3 or 4 talazoparib-related toxicities. Patients must receive their first dose of talazoparib in this protocol within 2 months after their last dose of talazoparib in the originating study and may not receive any intervening antineoplastic therapies before starting this study. Patients will have clinic visits approximately every 4 weeks for the first 24 weeks and then approximately every 8 weeks thereafter or as clinically indicated (patients enrolling from study PRP-001 may continue the last visit schedule they tolerated in that study). Additional clinic visits and laboratory testing may be necessary to monitor safety (i.e., for dose modification, hematologic toxicity, pregnancy testing).

The maximum starting dose of talazoparib will be 1 mg/day or the last tolerated dose administered in the originating study. Talazoparib capsules will be administered by mouth once daily with or without food at approximately the same time of day. Patients receiving talazoparib as combination treatment in the originating study will receive talazoparib as a single agent in this extended treatment study. Talazoparib administration may continue as long as the investigator considers treatment to be beneficial or until other study

discontinuation criteria are met. The addition of any other antineoplastic therapy and the concurrent use of investigational agents during the study are prohibited.

The study design is summarized graphically in Figure 1.

Figure 1. Overall Study Design



Key assessments: laboratory tests, physical examinations, adverse events.
Patients enrolling from study PRP-001 may continue the last visit schedule they tolerated in that study.

Approximately 150 patients who may benefit from continuing therapy with talazoparib will be enrolled in this extended treatment study from qualifying talazoparib clinical studies in advanced solid tumors sponsored by Medivation (a wholly owned subsidiary of Pfizer Inc.). Studies include a phase 1 dose-escalation study (PRP-001) and 5 short-duration clinical pharmacology studies.

3. ENDPOINT AND BASELINE VARIABLES

3.1. Baseline Variables

The baseline characteristics include:

- Age
- Sex
- Race
- Height
- Weight
- Eastern Cooperative Oncology Group (ECOG) performance status
- Primary diagnosis
- Prior surgeries
- Prior systemic anti-cancer therapies
- Prior radiotherapy

3.2. Safety Endpoints

3.2.1. Adverse Events

All adverse events will be graded by the Investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4 and coded by system organ class (SOC) and preferred term (PT) based on Medical Dictionary for Regulatory Activities (MedDRA). The latest version of MedDRA available at the time of the final analyses will be used for reporting the results of the study and the version number will be specified in the clinical study report (CSR).

3.2.2. Laboratory Data

Laboratory data in this study consist of hematology and blood chemistry values. All clinical laboratory tests will be performed by the local laboratory. Laboratory values will be classified by severity using the CTCAE version 4, as appropriate.

3.2.3. Vital Signs and Weight

Temperature, blood pressure (systolic and diastolic), weight, and heart rate will be collected at baseline and each subsequent scheduled assessment.

4. ANALYSIS POPULATIONS

4.1. Screened Population

Screened population includes all patients who have signed the informed consent form (ICF) and completed the screening phase.

4.2. Safety Population

Safety population includes all patients who receive any amount of talazoparib.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Definitions

5.1.1. Study Drug

The study drug is talazoparib (ie, PF-06944076, MDV3800), which is self-administered daily for as long as the investigator considers treatment to be beneficial or until other study discontinuation criteria are met.

5.1.2. Date of First Dose

Date of first dose is the first date when a non-zero dose of talazoparib is administered in the treatment phase.

5.1.3. Study Day

Study day will be calculated in reference to the date of first dose.

For assessments conducted on or after the first dose, study day is calculated as (assessment date – first dose date + 1).

For assessments conducted before the first dose date, study day is calculated as (assessment date – first dose date).

The study day will be displayed in all relevant data listings.

5.1.4. Treatment-Emergent Period

The treatment emergent period is defined as the duration of time from the first dose of talazoparib through approximately 30 days after the last dose (ie, permanent discontinuation) or before initiation of a new antineoplastic therapy, whichever occurs first.

5.1.5. Baseline and Post-baseline Values

Baseline is the non-missing measurement of an investigation obtained during the period from the date of signing an ICF to the start date of study treatment or an assessment to be collected post-dose on Week 1, whichever occurs first. If patients have no result as defined above, the baseline value will be missing.

Post-baseline values are defined as any measurements after the start date of study treatment, if applicable, but to exclude any baseline result taken on Week 1 as defined above.

Change from baseline is defined as (post-baseline value – baseline value).

5.1.6. Initial and Durable Dose Levels

The initial dose level is defined as the last tolerated dose given as the daily dose in the originating study.

The durable dose level is defined as the daily dose taken for the longest duration during the extended treatment period in this study.

5.1.7. Study Visits

Study visits will be determined from the scheduled times as reported on the electronic case report form (eCRF) for the summarization and analysis of data that are shown by study visits unless otherwise specified.

Study assessments including clinical laboratory tests, physical examinations, and vital signs will be performed every 4 weeks through week 25 and every 8 weeks thereafter during the study. Complete blood count (CBC) tests will be completed every 2 weeks through week 9 and every 4 weeks thereafter. Women of childbearing potential must have a pregnancy test every 4 weeks. Patients enrolling from study PRP-001 may continue the last visit schedule they tolerated in that study.

All treatment period visits have a visit window of ± 7 days (ie, 7 days before or after the given day), except the week 1 visit (assessment of eligibility and start of study treatment), which has a visit window of -28 days.

5.2. Standard Derivations and Reporting Conventions

Descriptive statistics (the number of patients [n], mean, standard deviation [SD], median, minimum, and maximum) will be used to summarize continuous variables. Means will be presented to 1 more decimal place than the recorded data. Medians will be presented using the same number of decimal places as the recorded data unless the calculated median results in an additional decimal place ending in '5' (i.e., 5 and 7 = 6, 5 and 8 = 6.5, etc.). Standard deviations will be presented to 2 more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data.

Frequency distributions (number [n] and percentage of patients [%]) will be used to summarize categorical or qualitative variables. In general, the denominator for the percentage calculation will be based upon the total number of patients in the study population for that particular time point assessment. Records that are missing or not done will not be factored into the percentage calculation, unless otherwise specified.

Percentages will be presented to a maximum of 1 decimal place.

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Year is calculated as (days/365.25) rounded up to 1 significant digit
- 1 month = 30.4375 days. Month is calculated as (days/30.4375) rounded up to 1 significant digit
- Age will be calculated as the integer relative to the patient's signed informed consent date and Date of Birth.
- 1 pound = 0.454 kg
- 1 inch = 2.54 cm
- Missing data will not be imputed unless otherwise specified
- For laboratory results collected as < or > for a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value
- For safety analyses, percentages will be calculated based on the number of patients in the safety population
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator unless otherwise specified
- Medical history and adverse events will be coded using the MedDRA.

  Prior therapies and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

5.3. Handling of Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

The imputed dates for adverse events will be used to determine the treatment-emergent period. For adverse events with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end date of the treatment-emergent period to determine if the event is treatment emergent. When in doubt, the adverse event will be considered treatment emergent by default.

The following rules will be applied to impute partial dates for adverse events:

- If start date of an adverse event is partially missing, impute as follows:
  - If both month and day are missing and year = year of treatment start date, then set to treatment start date
  - If both month and day are missing and year ≠ year of treatment start date, then set to January 1
  - If day is missing and month and year = month and year of treatment start date, then set to treatment start date
  - If day is missing and month and year ≠ month and year of treatment start date, then set to first of the month
  - If start date is completely missing, set to treatment start date as long as adverse event end date is not prior to treatment start date
- If end date of an adverse event is partially missing, impute as follows:
  - If both month and day are missing, then set to December 31
  - If only day is missing, then set to last day of the month
  - If end date is completely missing, do not impute

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). The following rules will be applied to impute partial dates for medications:

- If start date of a medication is partially missing, impute as follows:
  - If both month and day are missing, then set to January 1
  - If only day is missing, then set to the first of the month
- If end date of a medication is partially missing, impute as follows:

  - If both month and day are missing, then set to December 31
  - If only day is missing, then set to last day of the month
- If start date or end date of a medication is completely missing, do not impute

Listings will show the original date information without imputation, but derived parameters (treatment-emergent adverse event indicator and duration of adverse events) will be flagged.

6. ANALYSES AND SUMMARIES

6.1. Baseline Summaries and Other Analyses

6.1.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and tabulated by qualifying originating clinical study for the safety population. The variables to be included in the summary are age, sex, race, ethnicity, baseline body weight, height, and body mass index (BMI). Age in years will be calculated as the whole number of years between the date of birth and the date of informed consent.

Cancer diagnosis, disease characteristics and ECOG performance status will be summarized using frequency counts and percentages.

Note: Demographics and baseline disease characteristics can be obtained from the corresponding eCRF page collected in the originating clinical studies (ie, PRP-001, MDV3800-01 [C3441001], MDV3800-2 [C3441002], MDV3800-03 [C3441003], MDV3800-04 [C3441004], and MDV3800-14 [C3441005]).

6.1.2. Medical History

Verbatim medical history terms collected will be coded by SOC and PT based on MedDRA coding dictionary. The latest version of MedDRA available at the time of the final analyses will be used for reporting the results of the study and the version number will be specified in the clinical study report (CSR).

The number and percentage of patients with at least one medical history will be summarized by SOC and PT and tabulated by qualifying originating clinical study for the safety population.

All medical history data will be provided in a listing.

6.1.3. Enrollment Status

All inclusion/exclusion criteria met, not met, or not done will be provided in listings. These listings will also provide any eCRF data collected detailing the allowance of patients into a study if at least one inclusion/exclusion criterion is not met.

Additional patient informed consent and eligibility information collected on the eCRF will be also provided in a listing.

6.1.4. Patient Disposition

Patients included in the safety populations, who completed the study, discontinued with reasons for treatment discontinuation will be summarized and listed as well.

6.1.5. Protocol Deviations

Patients with major protocol deviations will be listed and categories of major deviations include at least one of the following:

- Eligibility criteria not met
- Excluded concomitant medication taken
- Informed consent not signed before study-specific procedures were performed

A detailed list of all major protocol deviations will be determined before the database lock and a listing of all major deviations will be provided.

6.1.6. Study Treatment Exposure and Compliance

The initial dose level from qualifying originating studies and the durable dose level given during extended treatment period in this study will be summarized for the safety population.

Patient exposure and compliance to study drug will be presented by durable dose level, and the variables include duration of exposure in months, number of capsules taken and percent compliance.

Treatment compliance will be assessed based on patients' used and unused study drug containers and their completed study drug diary. Dose administration and treatment compliance will be listed for all patients.

6.1.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO-DD, and will be classified according to the default Anatomical Therapeutic Chemical (ATC) classification system code, WHO-DD Drug Name, and PT.

Depending on the start and stop dates of the medication, it is possible for a medication to be both prior and concomitant.

Prior and concomitant medications will be summarized by the highest ATC class level and PT by treatment group for the safety population. Patients may have more than one medication per ATC category and PT. At each level of patient summarization, a patient will be counted once if he/she reports one or more medications at that specific level.

All medications will be presented in a data listing.

6.2. Safety Summaries and Analyses

6.2.1. Adverse Events

An adverse event will be considered treatment-emergent adverse event (TEAE) if the onset date occurred on or after the administration of first dose of study drug through approximately 30 days after the last dose. A study drug-related TEAE is defined as any TEAE with at least a possible relationship to the study drug as assessed by the investigator or that is missing the assessment of causal relationship whose relationship to the study drug could not be ruled out.

Summaries including the number of patients and percentages of the following adverse events will be provided:

- Overview of TEAE
- TEAE by SOC and PT
- TEAE by decreasing frequency of PT
- TEAE related to study drug by SOC and PT
- TEAE related to study drug by decreasing frequency of PT
- TEAE by SOC, PT, and maximum severity
- Serious TEAE by SOC and PT
- Serious TEAE related to study drug by SOC and PT
- TEAE leading to study drug discontinuation by SOC and PT
- TEAE leading to death by SOC and PT

All AEs will be listed with its relationship to study drug and severity, flagging those which are not events during treatment-emergent period.

A listing of all deaths with date, cause and its relationship to study drug will be also listed.

6.2.2. Laboratory Data

Quantitative laboratory test results and their change from baseline will be summarized by scheduled visit. Shift tables using CTCAE grades will be provided to compare the baseline with the worst post-baseline toxicity. The latest non-missing measurement taken on or before Week 1 will be used as baseline.

Liver tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline Phosphatase (ALP), and total bilirubin (TBL) are used to assess possible drug induced liver toxicity. The ratios of test result over the upper limit of normal (ULN) will be calculated and classified for these parameters. The number and percentage of patients with each of the following categories will be summarized:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- ALT or AST ≥ 3xULN
- ALT or AST > 5xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- ALT or AST ≥ 3xULN and TBL > 2xULN
- ALT or AST ≥ 3xULN and TBL > 2xULN and ALP < 2xULN
- Concurrent or within 14 days ALT or AST ≥ 3xULN and TBL > 2xULN
- Concurrent or within 14 days ALT or AST ≥ 3xULN and TBL > 2xULN and ALP < 2xULN

Concurrent measurements are those occurring on the same date.

All laboratory data will be provided in data listings.

6.2.3. Vital Signs and Weight

Change from baseline will be calculated and presented at scheduled postbaseline assessments for each vital sign parameter (ie, temperature, systolic and diastolic blood pressure, heart rate, weight). The latest non-missing measurement taken on or before Week 1 will be used as baseline.

Clinically notable changes in vital signs results will be summarized using frequency counts and percentages.

Vital sign data will be provided in a listing.

7. INTERIM ANALYSES

N/A

8. REFERENCES

No literature reference is cited.