## Statistical Analysis Plan

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| Study code | D4881C00024 |
| Version | 2.0 |
| Date | 17 February 2020 |

# A Rollover Protocol For Patients Who Received Tremelimumab (CP-675,206) In Other Protocols

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| DOCUMENT: | Statistical Analysis Plan |
| PROTOCOL Number: | D4881C00024 |
| Title: | A Rollover Protocol For Patients Who Received Tremelimumab (CP-675,206) In Other Protocols |
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| PREPARED BY: | Quality Data Services, Inc. |

**SIGNATURES/APPROVAL PAGE**

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Date

**APPROVERS**

[redacted]

4Mar20
Date

## TABLE OF CONTENTS

## 1. LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse Event |
| ANC | Absolute Neutrophil Count |
| ALT | Alanine Aminotransferase |
| ALP | Alkaline Phosphatase |
| AST | Aspartate Aminotransferase |
| BUN | Blood Urea Nitrogen |
| CI | confidence interval |
| CRF | Case Report Form |
| CRP | C reactive protein |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Event |
| CTLA4 | cytotoxic T lymphocyte-associated antigen 4 |
| DAI | Dosage and Administration Instructions |
| ECG | electrocardiogram |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IV | intravenous |
| LDH | lactic acid dehydrogenase |
| RBC | red blood cell |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |

| Abbreviation or special term | Explanation |
|---|---|
| SD | standard deviation |
| SGOT | serum glutamic-oxaloacetic transaminase (AST) |
| SGPT | serum glutamic-pyruvic transaminase (ALT) |
| T3 | triiodothyronine |
| T4 | thyroxine |
| TEAE | Treatment-emergent adverse event |
| TLF | Tables, listings, figures |
| TSH | thyroid-stimulating hormone |
| ULN | upper limit of normal |
| WBC | white blood cell count |

# 2. INTRODUCTION

## 2.1. Objective of the Statistical Analysis Plan

This statistical analysis plan (SAP) describes the planned analysis of the safety and efficacy data from the study. A detailed description of the planned tables, figures and listings (TFLs) to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL template document.

The intent of this document is to provide guidance for the analysis of data related to safety and efficacy to describe any applicable statistical procedures. In general, the analyses come directly from the protocol, unless they have been modified by agreement between the Sponsor and [redacted] A limited amount of information concerning this study (e.g., objectives, study design) is summarized to help the reader interpret the accompanying TFL templates. That information is not a synopsis of the study and does not require review or approval because it is simply extracted from the protocol. Attached signatures indicate approval of the statistical analysis sections of the SAP, as well as accompanying TFL templates. These sections must be agreed upon prior to database lock. When the SAP and TFL templates are agreed upon and finalized, they will serve as the template for a portion of this study's clinical study report.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the appropriate section of the CSR. Any substantial deviations from this SAP will be agreed upon between the sponsor and [redacted] Deviations from this SAP, both substantial and non-substantial, will be documented in the CSR. Any updates to their respective analyses, study designs, and TFL presentations after this SAP is finalized and approved will be documented in a running Note to the SAP document.

Various outputs may be required during the conduct of this trial which will necessitate the production of some but not all of the Figures, Summary Tables and Key Data Tabulations detailed in this document. The SAP will not be updated to reflect these potential changes.

# 3. STUDY OBJECTIVES

The primary objective is:

- To allow access to tremelimumab (previously known as CP-675,206) for subjects who received tremelimumab in other trials.

The secondary objectives are:

- To follow long-term survival and tumor status of subjects treated with tremelimumab in other trials
- To monitor the safety and tolerability of tremelimumab

# 4. STUDY DESIGN

## 4.1. General Study Design and Plan

This is a multi-center, international, open label study.

## 4.2. Study Population

Eligible subjects are those who have received tremelimumab in another protocol but are no longer going to receive tremelimumab in the other trial. All subjects who are enrolled in this trial will have the opportunity to receive tremelimumab. Doses may be delayed under certain circumstances at the discretion of the investigator. Subjects not receiving tremelimumab should be seen in the clinic or contacted at least every 6 months to determine their tumor status until the time of final analysis.

## 4.3. Treatment Administration and Duration of Treatment

Subjects who received a single dose of tremelimumab or who received 15 mg/kg every 90 days in another study will receive intravenous administration of tremelimumab at a dose of 15 mg/kg on Day 1 of each 90-day cycle. To allow for possible change in body weight over time, subjects will be weighed within 10 days prior to each cycle and the administered dose of tremelimumab will be recalculated.

Subjects who have been receiving a different dosing regimen of tremelimumab in a prior study may have the option of continuing with the prior dosing regimen or of switching to the regimen of 15 mg/kg each 90 days.

For subjects on a 90-day or 3-month dosing regimen, doses should not be given less than 86 days from the previous dose. For subjects on other schedules, doses will not be given before 2 days prior to the scheduled dose.

Doses may be delayed under certain circumstances at the discretion of the investigator. Subjects not receiving tremelimumab should be seen in clinic or contacted at least every 6 months to record their tumor status until the time of final analysis.

No dose reduction of tremelimumab is permitted in the study.

Dose delays and re-dosing criteria for tremelimumab based on laboratory parameters and based on treatment-related adverse events are described in Section 5.2.3.2 of the protocol.

Dose stopping rules for adverse events are included in Section 5.2.3.3 of the protocol.

### 4.4. Trial Procedures

This study includes a screening period followed by a treatment period with multiple cycles. See Appendix A for the schedule of assessments and activities for each period and cycle.

Subjects will be followed for at least 90 days after the last dose of study drug for reportable adverse events. If there is evidence of continuing study drug-related toxicity, subjects will continue to be followed at intervals deemed medically appropriate by the investigator.

### 4.5. End of treatment

Subjects may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator is to inquire about the reason for withdrawal, to request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

The following are possible reasons for discontinuation from treatment:

1. Withdrawal due to adverse event.
2. Disease progression, unless there is reasonable evidence of clinical benefit to justify continuation on protocol.
3. Subjects may decide to withdraw from treatment at any time. Subjects who withdraw from treatment should be followed for tumor assessment and survival. If the subject also withdraws consent for disclosure of future information, no further evaluations should be

performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

4. Subjects who begin new investigational therapy, chemotherapy, or other therapy for his/her disease must not receive further treatment.
5. Subjects may be discontinued from the study for poor compliance at the discretion of the investigator.
6. The investigator should withdraw the subject at any time if he/she believes it is in the subject's best interest to do so.
7. The subject is lost to follow-up.
8. The study is terminated by the sponsor.

Data collection will be stopped, the database locked and the available data summarized once eligible patients are no longer available to enter the trial, and all patients have had the opportunity to be followed up for approximately 9.5 years. At this time AstraZeneca will continue to supply open-label drug to these patients, up to the time that they discontinue the treatment for whatever reason.

## 5. EFFICACY MEASUREMENTS

Efficacy measurements include tumor assessment and overall survival.

### 5.1. Tumor Assessment

The subject's tumor will be assessed according to the investigator's usual practice. The subject's tumor status (alive with disease [AWD] or no evidence of disease [NED]) and the date and type of the most recent tumor assessment should be recorded at each dosing visit and follow-up visit.

### 5.2. Overall Survival

Subject's survival will be monitored throughout the trial. After withdrawal from study treatment, subjects (or their physician) will be seen or contacted at least every 6 months to collect information on date of death and cause of death. This information can also be obtained by telephone interview.

## 6. SAFETY MEASUREMENTS

Safety will be evaluated by

- All adverse events
- Serious adverse events
- Grade 3 or 4 tremelimumab – related adverse events

- Immune-mediated adverse events
- Hypersensitivity reactions to tremelimumab
- Clinical laboratory tests,
- Vital signs measurements

### 6.1. Adverse Events

Details about adverse events definitions and reporting requirements are included in Section 8 of the protocol. Adverse events will be assessed throughout treatment period and during follow-up.

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to: abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity.

Additionally, they may include the signs or symptoms resulting from: drug overdose, drug withdrawal, drug abuse, drug misuse, drug interactions, drug dependency, extravasation, exposure in utero.

Worsening of signs and symptoms of the malignancy under trial will be reported as adverse events.

A treatment-emergent adverse event (TEAE) is defined as any sign or symptom that emerges during treatment, having been absent at pretreatment; or re-emerges during treatment, having been present at pretreatment but stopped prior to treatment; or worsens in severity during treatment relative to the pretreatment state, when the AE is continuous. Adverse events that started after a subject‘s last dose but within 7 days of dosing are considered treatment-emergent.

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that: results in death; is life-threatening (immediate risk of death); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; results in congenital anomaly/birth defect.

Progression of the malignancy under trial (including signs and symptoms of progression) will not be reported as a serious adverse event unless the outcome is fatal during the trial or within the safety reporting period. Hospitalization due to signs and symptoms of disease progression will not be reported as serious adverse event. If the malignancy has a fatal outcome during the trial or within the safety reporting period, then the event leading to death will be reported as an adverse event and as a serious adverse event with CTC Grade 5.

Severity assessment of adverse events:

| GRADE | Clinical Description of Severity |
|---|---|
| 0 | No Change from Normal or Reference Range |
| 1 | MILD Adverse Event |
| 2 | MODERATE Adverse Event |
| 3 | SEVERE Adverse Event |
| 4 | LIFE-THREATENING OR DISABLING Adverse Event |
| 5 | DEATH RELATED TO Adverse Event |

If adverse event severity is missing, the respective adverse event will be considered severe.

Causality will be determined for all adverse events (serious and non-serious) by the investigator. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the investigator's final determination of causality is unknown, then the event will be handled as "related to investigational product".

Withdrawal due to insufficient response will not be reported as withdrawal due to adverse events.

Immune-mediated adverse events are those adverse events for which the investigator was not able to rule out other possible etiologies.

### 6.2. Hypersensitivity Reactions to Tremelimumab

The following constitute hypersensitivity reactions to tremelimumab:

- CTCAE v.3.0 Grade 1 Allergy (transient flushing or rash, drug fever <38°C)
- CTCAE v.3.0 Grade 2 Allergy (urticaria, drug fever ≥38°C, and/or asymptomatic bronchospasm)
- CTCAE v.3.0 Grade 3 or 4 Allergy (symptomatic bronchospasm requiring parenteral medication(s) with or without urticaria; allergy-related edema/angioedema; hypotension; anaphylaxis)

These will be monitored and recorded throughout the study.

### 6.3. Clinical Laboratory Assessments

The protocol specifies the following: Laboratory assessments will be performed at baseline (up to 10 days before dosing in the first cycle) and within 10 days prior to each administration of tremelimumab. They include the following: lipase and amylase; liver function tests including AST (SGOT), ALT (SGPT), Alkaline Phosphatase (ALP), Gamma-Glutamine Transferase (GGT), lactic acid dehydrogenase (LDH); thyroid function tests including T3, T4, and TSH. Investigators will use the results of the laboratory tests to make re-dosing decisions. All women of childbearing potential will have a serum or urine pregnancy test completed within 10 days prior to each administration of tremelimumab.

The study database does not include laboratory tests results; therefore these will not be summarized for the clinical study report.

### 6.4. Vital Sign Measurements

Vital signs will be measured at on Days 1 on each cycle and will include: temperature, sitting systolic and diastolic blood pressure, and heart rate. These vital signs will be recorded prior to treatment and monitored as needed during drug infusion and for approximately 1 hour post-infusion. Height and weight will be collected before Cycle 1. To allow for possible change in body weight over time, subjects will be weighed within 10 days prior to each cycle.

### 6.5. Subject History

The subjects' prior history includes their cancer history, medical history, and dates of first and most recent tremelimumab administration.

## 7. GENERAL STATISTICAL CONSIDERATIONS

Statistical analysis and programming of tables and listings will be conducted by [redacted], using [redacted].

### 7.1. Determination of Sample Size

The number of subjects enrolled in this open-label single-treatment arm study will be determined by the number of subjects who received tremelimumab in other tremelimumab trials who wish to participate and who meet the eligibility criteria.

### 7.2. Methodology

No statistical methods will be employed to test a specific hypothesis in this study. Only descriptive statistics will be provided for safety and survival endpoints.

Continuous data will be summarized with the following descriptive statistics: number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarized with counts and percentages.

Data listings will be presented by subject and all data will be presented. Tables will be presented summary results for all subjects included in the study.

### 7.3. Handling of Dropouts or Missing Data

No data imputation will be done for safety parameters except for the adverse events (AEs) with missing starting date, missing severity or missing causality. If the AE onset date is unknown, then the date of first study treatment will be used for classification of TEAEs that were experienced following administration of study drug. If adverse event severity is missing, the respective adverse event will be considered severe. If the investigator's final determination of causality is unknown, then the event will be handled as "related to investigational product".

### 7.4. Multi-center Studies

This is a multi-center study. Study center will be displayed in the data listings. Summary tables will present results for all subjects enrolled in the study. There are no planned summary results by investigative center or by country.

### 7.5. Endpoints

#### 7.5.1. Efficacy Endpoints

Tumor Status: The subject's tumor will be assessed according to the investigator's usual practice. The possible results for disease status are: evidence of disease, no evidence of disease, indeterminate.

Overall Survival: Subject's survival will be assessed throughout the study from the first dose till the last contact during follow-up post last dose in the last cycle. After withdrawal from study treatment, subjects will be seen or contacted at least every 6 months to collect information on date of death and cause of death. Subjects or their physicians may be contacted via phone to collect information on date of death and cause of death. Subjects lost to follow-up will be censored at the time of the last available contact.

Disease Free Survival will be defined as the time from the first study drug dose to the earliest date of evidence of disease (based on tumor status assessment) or death, whichever occurs first.

#### 7.5.2. Safety Endpoints

The following safety endpoints will be summarized for the clinical study report:

- All adverse events
- Serious adverse events

- Grade 3 or 4 tremelimumab – related adverse events
- Hypersensitivity reactions to tremelimumab
- Vital signs measurements
- Concomitant medications

### 7.6. Analysis Populations

#### 7.6.1. Safety Population

The safety population is defined as all subjects treated with at least one dose of tremelimumab during the study. All safety data collected up to the end of the study (i.e., through the last follow-up evaluation) are included in the safety and efficacy analyses.

### 7.7. Demographics

The following demographic data: age, height, screening body weight will be summarized descriptively as number of subjects, mean, SD, median, minimum, and maximum. Gender and race will be summarized as counts and percentages.

### 7.8. Subject Disposition

The number of subjects enrolled in the study and included in the safety population will be presented overall, by investigative site, and by previous tremelimumab trial.

Eligibility (inclusion /exclusion) criteria will be listed by subject indicating if all criteria were met and if not, which ones were not met.

Subject disposition at the end of the study will be summarized as: completed or withdrawn. The number of subjects withdrawn from the study will be reported as count and percentage by reason.

### 7.9. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®) and summarized by system organ class and preferred term for all subjects in the safety population. Medical history reported terms, status (past/present), and other pertinent details will be included in the by subject data listing.

### 7.10. Duration of Treatment and Exposure to Study Drug

Duration of participation in the study (days) will be defined as date of last contact (visit or phone) – date of the first dose in the study + 1.

Duration of exposure (dosing) = date of the last dose – date of the first dose + 1. This will include any unplanned dose interruptions.

Duration of participation in the study will be summarized as number of subjects, mean, SD, median, minimum, and maximum for all subjects. Duration of exposure will be summarized as number of subjects, mean, SD, median, minimum, and maximum overall and by planned dose.

Since tremelimumab will be administered in the clinic by study personnel, compliance with study drug will not be computed.

### 7.11. Efficacy Analyses

All efficacy analyses will be performed using safety population. There are no statistical hypotheses tested in the study. Efficacy endpoints will be summarized using descriptive statistics only.

Tumor status results will be summarized (counts and percentage) by cycle/visit.

Survival will be summarized using Kaplan Maier estimate for median time and 95% confidence interval. Death is considered to be the "event" for Kaplan Meier analysis. Subjects who are lost to follow-up will be censored at the time of the last known contact. All other subjects will be censored at the time of study completion.

Disease free survival will be summarized using Kaplan Maier estimate for median time and 95% confidence interval. Evidence of disease (based on tumor status assessment) or death are considered to be the "event" for Kaplan Meier analysis. "Event" date will be date when the subject's assessment for tumor is "evidence of disease" or date of death, whichever comes first. Subjects who are alive and without evidence of disease or who are lost to follow-up will be censored at the time of the last tumor assessment date on or prior to the last known contact. All other subjects will be censored at the time of study completion.

### 7.12. Safety Analysis

All safety analyses will be conducted on subjects who received at least one dose of protocol therapy (Safety Population). The safety evaluations to be summarized include: AEs, vital signs, and concomitant medications.

Safety results will be reported using summary tables and by subject data listings. Continuous variables will be summarized using mean, SD, median, minimum, and maximum. Categorical variables will be summarized by presenting the number (frequency) and percentage in each category.

If any screening safety data is repeated, the measurement taken closest to dosing will be used in the analysis as pre-study baseline. If any post-dose safety data is repeated the measurement taken first at the particular visit will be used in the analysis.

#### 7.12.1. Prior and Concomitant Medications

Prior and concomitant therapies as recorded on the CRF will be coded to a World Health Organization Drug Dictionary (WHO- DD) term.

Prior medications are all doses taken prior to the first dose of study medication. Concomitant medications are all doses taken after the first dose of study medication. If any medications were started prior to dosing and were continued after dosing they will be shown in the Prior\Concomitant Medications listings and will be included in the concomitant summary table.

The use of concomitant medications will be summarized as number and percentage of subjects taking each medication by ATC Classification.

### 7.12.2. Adverse Events

Adverse events (AEs) that occur after administration of the first study dose until completion of the follow up evaluations will be considered treatment-emergent (TEAE). If the start date of the AE is unknown, it will be assumed to be treatment-emergent. TEAEs will be summarized by system-organ-class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency of subjects who experience TEAEs will be summarized overall. Subjects, having the same AE more than once per group, will be counted once for each preferred term and once within each system organ class.

Separate summary tables (number of subjects and percentage) will be prepared for:

- Serious adverse events
- Grade 3 or 4 tremelimumab related adverse events
- Hypersensitivity reactions to tremelimumab:
    - CTCAE v.3.0 Grade 1 Allergy (transient flushing or rash, drug fever <38°C);
    - CTCAE v.3.0 Grade 2 Allergy (urticaria, drug fever ≥38°C, and/or asymptomatic bronchospasm);
    - CTCAE v.3.0 Grade 3 or 4 Allergy (symptomatic bronchospasm requiring parenteral medication(s) with or without urticaria; allergy-related edema/angioedema; hypotension; anaphylaxis).

All deaths will be included in a separate by subject data listing which will include date of death, cause of death (including specifics for study treatment toxicity, if applicable). Deaths may also be summarized by cause of death.

All AEs are listed by subject, including non-treatment-emergent (i.e., pre-dosing or post-dosing) AEs, if applicable. Separate by subject data listings will be provided for subjects who experience treatment-emergent SAEs and for TEAEs leading to early termination from the study.

Separate summary tables will display the number of subjects and percentage of with treatment-emergent AEs by maximum severity (grade), treatment-emergent AEs by relationship to study drug, and treatment-emergent AEs that led to premature discontinuation of study classified by system organ class and preferred term.

### 7.12.3. Vital Signs

Vital sign measurements will be summarized using descriptive statistics for each visit and measurement time. Individual change from baseline in vital sign measurements will be calculated and summarized descriptively. A by-subject listing of all vital sign measurements will be displayed. Unscheduled visits will only be displayed in the listings.

## 8. SUMMARY OF CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

SAP includes an additional efficacy endpoint included: Disease free survival.

Clinical laboratory test results are not available in the study database and no summary results and/or by subject data listings will be prepared for the study report.

## 9. REPORTING CONVENTIONS

The mean and median will be displayed to one decimal place greater than the original value and the standard deviation will be displayed to two decimal places greater than the original value. All statistical programming and analyses will be performed using [redacted]

The following standards will be used in the data presentation:

- Post-text tables should be in landscape format. Output should adhere to US / International Conference on Harmonization (ICH) margins and should not require changes for European page size. For post-text tables, a blank row will separate the header from the content of the table listing. For tables that have “n (%)”, the placement should be centered below “N=xx” in the column header. Frequency tables will be center justified. Descriptive statistics will be decimal aligned.

- Percentages presented in in-text tables should be rounded to one decimal using the SAS rounding function. If “%” is part of the column heading, do not repeat the “%” sign in the body of the table. Unless specified otherwise, “%” should reflect the total population of the treatment groups. Any deviation from that should be part of the footnote. For 0 counts, leave the corresponding percentage blank.

- The format for minimum and maximum should be "Min, Max". SD should be the default for representing scale, unless standard error has been specified. Standard deviation should be abbreviated as "SD", and presented next to the mean value, without any +/- sign. The SD should have one additional decimal place beyond that of the mean (e.g. mean has one decimal place, SD should have two).

- "N" will represent the entire treatment group for the population group being analyzed, while "n" will represent a subset of the treatment group. For tables with population designated as a row heading, "N" should be used (i.e. tables where all participant data is not available for every variable within a treatment group). As a guideline, if the number is used in a denominator it should be presented as "N". If the number is used in the numerator, it should be presented as an "n".

- The heading should consist of four lines. Line 1: Sponsor identifier. Line 2: Protocol identifier. Line 3: blank line. Line 4: Table/Appendix number Table Title – Population. The title for in-text tables should begin with the Table/Appendix number.

- All data listings will be sorted by Subject Number and time point (if applicable).

- The date format for all dates is DDMMMYYYY.

A solid line should appear both above and below the column headings of a table. A solid line should appear at the end of the table or at the bottom of each page if the table extends to more than one page. Footnotes should start after the bottom solid line.

## 10. REFERENCES

References are provided in the protocol.

## 11. TABLES, FIGURES, AND LISTINGS

Planned tables, listings and figures for the study report are included in a separate document.

## 12. APPENDIX A: SCHEDULE OF ASSESSMENTS AND ACTIVITIES

**Table 1 Schedule of Activities**

| D4881C00024 | | First Cycle [1] | | | Subsequent Cycles | | Follow-Up Off Tremelimumab Treatment [10] | |
|---|---|---|---|---|---|---|---|---|
| Protocol Activities | Prior to Enrollment | Up to 10 days before dose | Day 1 | Within 10 days prior to Day 1 of next cycle | Day 1 or up to 72 hours before dose | Within 10 days prior to next dose | 90 Days post-dose | Every 6 Months |
| SCREENING/BASELINE | | | | | | | | |
| Informed Consent [2] | X | | | | | | | |
| Contraception Counseling [3] | X | | | | | | | |
| Demographics | X | | | | | | | |
| Medical History | X | | | | | | | |
| SAFETY ASSESSMENTS | | | | | | | | |
| Adverse Event Assessment [4] | | | Post-dose | | X | | X | |
| Review Concomitant Medications [5] | | | X | | X | | | |
| Weight | | X | | X | | X | | |
| Vital Signs [6] | | | X | | X | | | |
| Pregnancy Test [7] | | X | | X | | X | | |
| Laboratory Assessments [8] | | X | | X | | X | | |
| STUDY TREATMENT | | | | | | | | |
| Review Redosing Criteria | | | X | | X | | | |
| Tremelimumab Administration | | | X | | X | | | |
| SURVIVAL AND TUMOR STATUS | | | | | | | | |
| Record Tumor Assessment [9] | | X | | X | | X | | X |
| FU for survival [10] | | | | | | | | X |

Footnotes:

| **Footnotes to Schedule of Activities:** |
|---|
| **1. Cycle:** For subjects on a 90-day (or 3-month) dosing regimen, doses should not be given less than 86 days from the previous dose. For subjects on other schedules, doses should not be given more than 2 days prior to the scheduled dose. |
| **2. Informed Consent:** All subjects must sign an informed consent document prior to any study-related procedures that are not considered standard of care. |
| **3. Contraception Counseling:** All women of childbearing potential must agree to practice a form of effective contraception for 12 months following any dose of study drug. |
| **4. Adverse Event Assessment:** Following the first dose, serious adverse events, tremelimumab-related grade 3 and 4 events, immune-mediated adverse events, and hypersensitivity reactions to tremelimumab should be assessed and documented during the study reporting period. See Section 8.2, Reporting Period. All reported study drug-related adverse events must be followed until the event has resolved, returned to baseline or has been deemed irreversible, or until the subject dies. |
| **5. Concomitant Medications:** Review medications taken by the subject since the last visit to determine whether treatment with tremelimumab is contraindicated. See Section 5.3, Concomitant Medications. |
| **6. Vital Signs:** Vital signs, including temperature, blood pressure (sitting), and heart rate. During tremelimumab infusions, routine monitoring of the subjects' blood pressure, heart rate, and temperature should be recorded prior to treatment and monitored as needed during drug infusion and for approximately 1 hour post-infusion. Patients experiencing symptoms or changes in their vital signs should be monitored more frequently as needed |
| **7. Pregnancy Test:** For women of childbearing potential. Serum or urine. Results must be available prior to dosing. Pregnancy tests may also be repeated during the study as per request of IEC/IRBs or if required by local regulations. Subjects who become pregnant must not receive further treatment while they are pregnant. |
| **8. Laboratory Assessments: Blood Chemistry:** Lipase, Amylase, AST (SGOT), ALT (SGPT), Alkaline Phosphatase (ALP), Gamma-Glutamine Transferase (GGT), Lactic Acid Dehydrogenase (LDH) **Thyroid Function:** T3, T4, TSH **Hematology:** WBC with differential count and Absolute Neutrophil Count (ANC), RBC count, Hemoglobin, Hematocrit, Platelet Count |
| **9. Tumor Assessment:** The results of any tumor assessments should be reviewed, and the tumor status (NED or AWD) and date of assessment should be recorded. If the patient begins a new treatment for their tumor, the start date and type of treatment will be recorded on the CRF. See Section 7.4 Tumor Assessments. |
| **10. Follow-Up:** Subjects (or their physicians) should be seen or contacted at least every 6 months to collect information on date of death, cause of death, and tumor status. If the patient begins a new treatment for their tumor, the start date and type of treatment will be recorded on the CRF. If there is evidence of continuing study drug-related toxicity, the subject should continue to be followed at intervals deemed medically appropriate by the investigator. This information may be obtained by telephone interview. |

## 13. DOCUMENT HISTORY

| Version Date | Modified By | Summary of Changes |
|---|---|---|
| Draft 2 | [redacted] | New efficacy endpoint included: Disease free survival |
| Version 1.0 | [redacted] | Removed analysis section for laboratory test results (not available in the database).<br>Included placeholder for Appendix B for Immune- mediated adverse events (to be finalized prior to dbase lock) |
| Version 1.1 | [redacted] (2020-01-23) | Updated to align with Protocol Amendment 2 (26 December 2019).<br>1. Replace CP-675,206 by tremelimumab<br>2. Removed "(former A3671024)" from Protocol number<br>3. Removed Dosing Hiatus<br>4. Removed Appendix B, List of Immune-Mediated Adverse Event |
| Version 1.1 | [redacted] (2020-02-17) | 1. Add amendment protocol stopping study section to SAP 4.5<br>2. Remove Immune mediated AE from safety endpoint, summary analysis, Appendix B from the SAP text |
| Version 2.0 | [redacted] (2020-03-03) | AZ requested to upgrade version from 1.1 to 2.0 to fit the publish system |