CLINICAL PROTOCOL

A ROLLOVER PROTOCOL FOR PATIENTS WHO RECEIVED TREMELIMUMAB (CP-675,206) IN OTHER PROTOCOLS

Compound:	CP-675,206
Compound Name (if applicable):	Tremelimumab
Sponsor	AstraZeneca AB, 151 85 Södertälje, Sweden
US IND Number (if applicable):	BB-10096
EudraCT number:	2008-000989-23
Protocol Number:	D4881C00024
Phase:	Phase 2
Version and Date:	Amendment 2 26 December 2019 Amendment 1 04 March 2008 Original Protocol 02 August 2006

SUMMARY

Indication:

This trial will enroll subjects who received tremelimumab (previously known as CP-275,206) in other trials and are no longer going to receive tremelimumab in the other trial.

Rationale:

Tremelimumab is a fully human monoclonal antibody. It binds to the CTLA4 molecule, which is expressed on the surface of activated T lymphocytes. The binding of CTLA4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Tremelimumab antagonizes binding of CTLA4 to B7 ligands and enhances human T-cell activation as demonstrated by increased cytokine (interleukin-2, interferon-gamma) production in vitro in whole blood or peripheral blood mononuclear cells cultures. Tremelimumab is thought to stimulate subjects' immune systems to attack their tumors by blocking a negative regulatory signal, as mentioned above.

The anti-tumor activity of antibodies to CTLA4 has been demonstrated in a variety of murine tumor models. Tremelimumab has also been shown to induce durable tumor responses in subjects with metastatic melanoma in Phase 1 and Phase 2 clinical studies.

More complete information is available in the current tremelimumab Investigator Brochure.

Objectives:

Primary Objective

- To allow access to tremelimumab for subjects who received tremelimumab in other trials

Secondary Objectives

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

Trial Design:

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

Endpoints:

Safety Endpoints

- Serious adverse events
- Grade 3 or 4 tremelimumab-related adverse events
- Immune-mediated adverse events
- Hypersensitivity reactions to tremelimumab

Efficacy Endpoints

- Tumor status: alive with disease (AWD) or no evidence of disease (NED)
- Survival

Trial Treatments:

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 should be weighed within 10 days prior to each cycle and the administered dose of tremelimumab should be recalculated.

Subjects who have been receiving a different dosing regimen of tremelimumab in a prior study may have the option of continuing with their prior dosing regimen or 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 dosing schedules, doses should not be given more than 2 days prior to the scheduled dose.

Doses may be delayed under certain circumstances at the discretion of the investigator:

- Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.

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 the final analysis.

Statistical Methods:

Sample Size

The number of subjects enrolled in this 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.

No statistical methods will be employed to test a specific hypothesis in this study. Only descriptive statistics will be provided for safety (number and percentage of subjects with adverse events) and survival (median, range, 95 percent confidence interval) end-points.

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 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.

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1 INTRODUCTION

1.1 Background

Rationale for tremelimumab (previously known as CP-675,206) in Melanoma and Other Tumors:

Tremelimumab is a fully human monoclonal antibody. It binds to the CTLA4 molecule, which is expressed on the surface of activated T lymphocytes. The binding of CTLA4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Tremelimumab antagonizes binding of CTLA4 to B7 ligands and enhances human T-cell activation as demonstrated by increased cytokine (interleukin-2, interferon-gamma) production in vitro in whole blood or peripheral blood mononuclear cells cultures. Tremelimumab is thought to stimulate subjects' immune systems to attack their tumors by blocking a negative regulatory signal, as mentioned above.

The anti-tumor activity of antibodies to CTLA4 has been demonstrated in a variety of murine tumor models. Tremelimumab has also been shown to induce durable tumor responses in subjects with metastatic melanoma in Phase 1 and Phase 2 clinical studies.

1.1.1 Rationale for this Trial

Tremelimumab has been and will be tested in multiple clinical trials. Each of the protocols allows the administration of a limited number of doses of tremelimumab. This rollover protocol will allow continued access to tremelimumab for subjects who have received it in other trials, until this agent becomes commercially available or development is discontinued.

Some subjects who were treated in early phase trials have experienced long term survival and/or durable tumor responses.[1] This protocol will allow long-term follow-up of subjects for survival and tumor status.

1.1.2 Clinical Data for Tremelimumab

The results of previous clinical trials are summarized in the current Investigators Brochure.

1.2 Tremelimumab Risks and Precautions

Risks with tremelimumab monotherapy include, but are not limited to, gastrointenstinal effects (colitis, diarrhea, enterocolitis, intestinal perforation, and large intestinal perforation); endocrine disorders (hypo- and hyperthyroidism, hypophysitis, and adrenal insufficiency); skin effects (rash and pruritus); lipase and/or amylase elevations and clinical manifestations of pancreatitis; hepatic events (including immune-mediated hepatitis and liver enzyme elevations); pneumonitis and ILD; neurotoxicity (including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barré syndrome); thrombocytopenia, anemia, and neutropenia; infusion-related reactions and hypersensitivity/anaphylactic reactions; renal events (including nephritis/autoimmune nephritis and acute kidney injury); autoimmune

arthritis, Sjogren's syndrome; giant cell temporal arteritis, and ulcerative colitis; and hyperglycemia and diabetes mellitus.

For information on all identified and potential risks for tremelimumab, please always refer to the current version of the tremelimumab IB.

In monotherapy clinical studies, AEs reported at an incidence of $\geq$ 20% include events such as diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, and vomiting. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab, and approximately 45% of patients experienced an SAE. Please see the current version of the tremelimumab IB for a detailed summary of tremelimumab monotherapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the tremelimumab program.

2 TRIAL OBJECTIVES

2.1 Primary Objective

- To allow access to tremelimumab for subjects who received tremelimumab in other trials

2.2 Secondary Objectives

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

3 TRIAL DESIGN

This is a multi-center, international, open label study. Eligible subjects are those who have received tremelimumab in another protocol but are no longer going to receive tremelimumab in the other trial. This protocol will allow continued access to tremelimumab for subjects who have received it in other trials, until this agent becomes commercially available or development is discontinued.

3.1 Endpoints

3.1.1 Safety Endpoints

- Serious adverse events
- Grade 3 or 4 tremelimumab-related adverse events
- Immune-mediated adverse events
- Hypersensitivity reactions to tremelimumab

3.1.2 Efficacy Endpoints

- Tumor status: alive with disease (AWD) or no evidence of disease (NED)
- Survival

4 SUBJECT SELECTION

It is expected that patients in ongoing trials will not be eligible except in extraordinary circumstances.

The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the trial:

1 The subject received tremelimumab in another protocol.
2 Females of childbearing potential must agree to practice a form of effective contraception for 12 months following any dose of study drug. The definition of effective contraception will be based on the judgment of the investigator.
3 Subject must be willing and able to provide written informed consent and to comply with scheduled visits and other trial procedures.

4.2 Exclusion Criteria

There are no exclusion criteria.

Note that subjects must meet all of the redosing criteria (Section 5.2.3.1 and 5.2.3.2) in order to receive any dose of tremelimumab in this study.

4.3 Randomization Criteria

The Sponsor must approve the enrollment of each patient. Subjects must withdraw from treatment in their other tremelimumab trial prior to enrollment in this study.

4.4 Life Style Guidelines

Females of childbearing potential must agree to practice a form of effective contraception for 12 months following any dose of study drug. The definition of effective contraception will be based on the judgment of the investigator.

5 TRIAL TREATMENTS

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 should be weighed within 10 days prior to each cycle and the administered dose of tremelimumab should 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 should not be given before 2 days prior to the scheduled dose.

Doses may be delayed under certain circumstances at the discretion of the investigator:

- Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.

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 the final analysis.

5.1 Allocation to Treatment

This is an open label trial. Allocation to study treatment will take place during the enrollment process. Please refer to the Study Manual for details.

Subjects must withdraw from treatment in their other tremelimumab trial prior to enrollment in this study.

5.2 Drug Supplies

5.2.1 Formulation and Packaging

Tremelimumab is supplied as a sterile solution, packaged in 20 mL clear glass vials with a rubber stopper and an aluminum seal. Each vial contains 20 mg/mL of tremelimumab (with a nominal fill of 400 mg per vial), in 20 mM Histidine buffer, pH 5.5, with 84 mg/mL Trehalose dehydrate, 0.2 mg/ml Polysorbate 80 and 0.1 mg/mL diSodiumEDTA dehydrate.

The standard supply of tremelimumab is delivered to the investigator site in a white carton with 4 vials of tremelimumab within foam inserts. The vial and carton labels identify tremelimumab as “tremelimumab (clonal), 20 mg/ml IV VialSolution 400 mg/vial”. The

lastest formulation, packaging and labeling will be provided in an updated Investigational Product Manual. Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

5.2.2 Preparation and Dispensing

Specific preparation instructions are provided in the most current version of the Investigational Product Manual. A member of the Pharmacy or Clinical Research Unit staff with appropriate training and experience must prepare all supplies.

5.2.3 Administration

Tremelimumab may be diluted with sterile normal saline (supplied by the investigator) prior to administration according to specific instructions in the Investigational Product Manual. Tremelimumab should be administered open label as an intravenous solution followed by observation. Specific dosing and administration instructions are provided in the most current version of the Investigational Product Manual.

Although tremelimumab is a fully human monoclonal antibody, immunogenicity remains a possibility, so acute and subacute hypersensitivity reactions are possible. 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.

Medications to treat hypersensitivity reactions should be available, such as IV saline, acetaminophen, and emergency drugs, including subcutaneous epinephrine, diphenhydramine, methylprednisolone, and nebulized albuterol. See Section 5.4.1 for guidelines on management of hypersensitivity reactions. If a hypersensitivity reaction attributed to tremelimumab occurs, the investigator must report this to the AstraZeneca study physician.

5.2.3.1 Dose Delays and Re-Dosing Criteria for Tremelimumab

The initiation of a cycle may be delayed to allow recovery from treatment-related toxicity.

There is a concern that subjects with active brain metastases may be at risk for increased intracranial pressure if treated with tremelimumab. Subjects with brain metastases must not receive tremelimumab until after the metastases have been adequately treated with surgery and/or radiation.

Subjects must not receive tremelimumab while pregnant or breast-feeding. Females of childbearing potential must have a negative serum or urine pregnancy test within 10 days prior to each dose. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential.

For details on dosing delays and re-dosing criteria, please refer to the Dosing Modification and Toxicity Management Guidelines, which is delivered as an Annex document.

5.2.3.2 Stopping Rules for Adverse Events

Subjects who experience any of the following adverse events at any time during the previous cycle must not receive further dosing with tremelimumab unless the investigator discusses the case with the AstraZeneca study physician and has provided a written action plan.

- Hypersensitivity to tremelimumab, Grade 3 (see Section 5.4.1)
- Hypersensitivity to tremelimumab, Grade 2, and symptoms reappear after infusion restarted
- Melanoma associated retinopathy, Grade 2 or above
- Uveitis, Grade 2 or above
- Diverticulitis
- Immune-mediated thrombocytopenia

5.2.4 Compliance

Tremelimumab will be administered in the clinic by study personnel. The dose administered will be recorded in the subject records and in the Case Report Form (CRF).

5.2.5 Drug Storage and Drug Accountability

Tremelimumab must be stored at 2°C to 8°C (36°F to 46°F). It is important that the formulation is not frozen. The investigator or an approved representative (e.g., pharmacist) must ensure that all study drug is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product(s). Drug accountability forms used must identify the investigational product, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to AstraZeneca.

At the end of the trial, AstraZeneca will provide instructions as to disposition of any unused investigational product. If AstraZeneca authorizes destruction at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by AstraZeneca. Destruction must be adequately documented.

5.2.6 Treatment after the End of the Study

After the final analysis, AstraZeneca will continue to supply open-label drug to patients receiving tremelimumab therapy up to the time that they discontinue the treatment for whatever reason (see Section 6.3). At the time of the final analysis and thereafter:

- Assessment will revert to standard of care at particular site
- There would be no more data collection except for SAE reporting. Clinical study database would be closed
- Paper form process would be used for SAE reporting. All SAEs, overdoses and pregnancies would be reported until 90 days after last dose
- Drug dispensation and reconciliation will be handled by site on each patient's visit
- Study would be opened until last patient treated. Final last subject last visit will be defined as last patient's treatment discontinuation

5.3 Concomitant Medication(s)

Concomitant medications to treat the subject's primary malignancy are not allowed unless these drugs were allowed in the subject's original protocol; AstraZeneca does not supply these concomitant medications for this protocol. Examples of allowed concomitant anti-cancer therapy include:

Table 2 Examples of Allowed Concomitant Anti-Cancer Therapies

Protocol #	Indication	Allowed Anti-Cancer Therapy
A3671006	Breast Cancer	exemestane (Aromasin)

Patients from Renal Cell Carcinoma studies should not receive sunitinib within 3 months of a dose of tremelimumab, as acute renal failure has been reported with combination therapy of tremelimumab and sunitinib. It is unknown whether there could be a safety issue with combination of tremelimumab and other tyrosine kinase inhibitors.

Since the anti-tumor activity of tremelimumab is thought to involve activation of the immune system, the use of immunosuppressive drugs should be avoided if alternative treatment is available. However, it is recognized that subjects may require immunosuppressive drugs such as corticosteroids for management of underlying disease, treatment-related toxicity, or unrelated conditions. Topical and inhaled corticosteroids in standard doses are not expected to be immunosuppressive.

It is highly recommended that subjects not receive anti-infective immunizations for at least 6 months after dosing with tremelimumab, given that the effect of the immunization has not been explored under conditions of CTLA4 blockade.

Concommitant medications should not be recorded on the Case Report Form unless they were administered to treat a **reportable** adverse event (See Section 8.1).

5.4 Management of Toxicity and Dose Modification Information of Tremelimumab

Comprehensive toxicity management guidelines have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitors durvalumab [Medi4736] (PD-L1 inhibitor) and tremelimumab (CTLA4 inhibitor). Given the similar underlying mechanisms of toxicities observed with these two compounds, these guidelines are applicable to the management of patients receiving either drug as monotherapy or in combination. Additionally, these guidelines are applicable when either drug is used alone or in combination and is administered concurrently or sequentially with other anti-cancer drugs (i.e. antineoplastic chemotherapy, targeted agents), as part of a protocol specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment. The most current version of the TMGs entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy" is provided to the investigative site as an Annex document and is maintained within the Site Master File.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related. In addition, there are certain circumstances in which tremelimumab should be permanently discontinued (see Section 5.2.3.2 of this protocol and the Dosing Modification and Toxicity Management Guidelines). Following the first dose of IP, subsequent administration of tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to tremelimumab monotherapy regimen by the reporting Investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

5.4.1 Management of Hypersensitivity Reactions to Tremelimumab

In case of hypersensitivity reactions, the Investigator should institute treatment measures deemed medically appropriate and notify the AstraZeneca Clinician of the event. The following treatment recommendations may be applicable and can be adopted at the investigator's judgment:[3, 4]

CTCAE v.3.0 Grade 1 Allergy (transient flushing or rash, drug fever <38°C):

- Supervise at the bedside.

CTCAE v.3.0 Grade 2 Allergy (urticaria, drug fever ≥38°C, and/or asymptomatic bronchospasm):

- Interrupt the infusion of tremelimumab and disconnect infusion tubing from subject.
- Administer IV antihistamines (diphenhydramine 25-50 mg and ranitidine 50 mg or cimetidine 300 mg).
- After recovery of symptoms, resume the infusion at half the initial infusion rate. If no further symptoms appear, complete the administration of the dose. If symptoms reappear, stop infusion and discontinue the subject from treatment.
- *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):*
- Stop the infusion of tremelimumab and disconnect infusion tubing from subject.
- Administer epinephrine (1:10,000) in 3.5 to 5 mL IV boluses (no more than 6 doses).
- Administer IV antihistamine (diphenhydramine 50 mg IV push).
- If wheezing persists: 0.35 mL of inhaled albuterol or other bronchodilators.
- Consider methylprednisolone 30 to 60 mg IV push, which may prevent recurrent or ongoing reactions.
- Discontinue the subject from treatment

5.4.2 Medication Errors

The definition of a Medication Error can be found in Appendix 4.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, i.e., immediately but no later than 24 hours after he/she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.2) and within 30 days for all other medication errors.

6 TRIAL PROCEDURES

6.1 Screening

Informed Consent

All subjects being considered for this study must sign an informed consent document prior to any study-related procedures that are not considered to be standard of care and prior to receiving study drug.

Screening assessments are outlined in

Table 1.

6.2 Treatment Period

All assessments for each cycle are outlined in

Table 1.

6.3 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 should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

The investigator must determine the primary reason for discontinuation from treatment in this study:

1. Withdrawal due to adverse event. When a discontinuation is due to a serious adverse event (SAE), the serious adverse event must be reported in accordance with the reporting requirements and the discontinuation must be reported immediately to the AstraZeneca clinical monitor or his/her representative.
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.

6.4 Follow-up Assessments

The post treatment follow-up assessments are outlined in

Table 1.

Subjects will be followed for at least 90 days after the last dose of study drug for reportable adverse events (See Section 8). 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.

After withdrawal from study treatment, 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. This information may be obtained by telephone interview.

In the event a subject is unable to return to the clinic for the follow-up visit, telephone contact with the subject (or their physician) to assess adverse events is expected. If laboratory assessments are needed to follow-up unresolved adverse events, retrieval of assessments performed at an institution local to the subject is acceptable.

The outcome of reportable adverse events with a date of onset during the study period should be reevaluated, and any new reportable adverse events should be recorded. All serious adverse events, and those reportable non-serious adverse events assessed by the investigator as possibly related to study drug should continue to be followed even after subject withdrawal from study. These adverse events should be followed until they resolve or until the investigator assesses them to be "chronic" or "stable."

7 ASSESSMENTS

The minimum required screening, on-study and follow-up subject assessments are summarized in the Schedule of Activities (

Table 1).

7.1 Baseline Demographics

Demographic data will include date of birth. The subject's prior tremelimumab study number and prior subject ID number in that study will be noted on the Case Report Form (CRF).

7.2 Subject History

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

7.3 Laboratories

Laboratory assessments will 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, TSH., hematology tests including WBC with differential count and Absolute Neutrophil Count (ANC), RBC count, Hemoglobin, Hematocrit, and Platelet Count. Investigators should review the results of all laboratory tests and use them to make re-dosing decisions.

All women of childbearing potential must have a serum or urine pregnancy test completed within 10 days prior to each administration of tremelimumab. The pregnancy test must be negative, and the 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.

Results of routine laboratory assessments will not be collected on the CRFs.

7.4 Tumor Assessments

The subject's tumor should 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.

Tumor status does not need to be recorded in the CRF for this protocol if it is being recorded in the CRFs as part of the post-treatment follow-up for the subject's prior protocol.

8 ADVERSE EVENT REPORTING

8.1 Adverse Events

The following adverse events must be reported as described in the subsequent sections.

- Serious adverse events
- Grade 3 or 4 tremelimumab-related adverse events
- Immune-mediated adverse events
- Hypersensitivity reactions to tremelimumab

For all adverse events which meet these criteria, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (See Section 8.5) requiring immediate notification to AstraZeneca or its designated representative. For all reported adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and AstraZeneca concurs with that assessment.

8.2 Reporting Period

8.2.1 Immediate Reporting of Serious Adverse Events

Serious adverse events require immediate notification to AstraZeneca or its designated representative beginning from the time that the subject provides informed consent for the study; and should be reported under the patient's prior protocol until the patient receives investigational product in this study. SAEs do not require notification if it has been at least 90 days since the previous dose of tremelimumab, and at least 28 days since any study-related procedures for the patient.

8.2.2 Reporting of Adverse Events on Case Report Forms

Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of trial treatment.

An adverse event does not need to be recorded in the CRF for this protocol if it is being recorded in the CRF for the patient's prior protocol.

If a subject begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3 Definition of an Adverse Event

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 should be reported as adverse events in the appropriate section of the CRF, providing they meet the reporting criteria in Section 8.1. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events.

8.4 Abnormal Test Findings

Abnormal objective test findings meeting the reporting criteria in Section 8.1 should also use the following criteria for determining whether an abnormal objective test finding should be reported as an adverse event:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5 Serious Adverse Events

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) should not be reported as an SAE unless the outcome is fatal during the trial or within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the trial or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTC Grade 5 (see Section 8.7, Severity Assessment).

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.[1]

8.6 Hospitalization

AEs reported from clinical trials associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;

[1] 21CFR 312.32

- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the trial protocol);
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery);
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.7 Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 3.0 document but may be used in certain circumstances.)
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

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.8 Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). 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 and the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on trial records.

In addition, if the investigator determines a serious adverse event is associated with trial procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.9 Exposure in Utero

For investigational products within clinical trials and for marketed products, an exposure inutero (EIU) occurs if:

1) a female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);

2) a male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

If any trial subject or trial subject's partner becomes or is found to be pregnant during the trial subject's treatment with the investigational product, the investigator must submit this information to AstraZeneca on an Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure to a AstraZeneca product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy.

The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify AstraZeneca of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting serious adverse events.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before an Exposure in Utero Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as serious adverse events follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to the investigational medication should be reported.

8.10 Withdrawal Due to Adverse Events (See also End of Treatment, Section 6.3)

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page if it meets the protocol-specified criteria for reportable adverse events.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.11 Eliciting Adverse Event Information

The investigator is to report all adverse events which meet the criteria for adverse event reporting in this trial (Section 8.1 including all directly observed adverse events and all adverse events spontaneously reported by the trial subject. In addition, each trial subject will be questioned about adverse events.

8.12 Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

All adverse events which meet the criteria for adverse event reporting in this trial (Section 8.1) will be reported on the adverse event page(s) of the CRF. An adverse event does not need to be recorded in the CRF for this protocol if it is being recorded in the CRF for the patient's prior protocol. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.12.1 Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, AstraZeneca is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to AstraZeneca must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of Exposure in Utero cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient trial subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to AstraZeneca in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by AstraZeneca to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to AstraZeneca or its designated representative.

8.12.2 Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events which meet the criteria for adverse event reporting in this trial (Section 8.1) are to be reported on the adverse event CRFs, which are to be submitted to AstraZeneca. An adverse event does not need to be recorded in the CRF for this protocol if it is being recorded in the CRF for the patient's prior protocol.

9 DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

The number of subjects enrolled in this study will be determined by the number of subjects who were administered tremelimumab in prior tremelimumab trials, who wish to participate in this trial and who meet the eligibility criteria.

9.2 Efficacy Analysis

No statistical methods will be employed to test a specific hypothesis in this study. Only descriptive statistics will be provided for survival (median, range, 95 percent confidence interval) end-points.

9.3 Safety Analysis

No statistical methods will be employed to test a specific hypothesis in this study. Only descriptive statistics will be provided for safety (number and percentage of subjects with adverse events) end-points.

9.4 Interim Analysis

Not Applicable

9.5 Data Monitoring Committee

Not Applicable

10 QUALITY CONTROL AND QUALITY ASSURANCE

During trial conduct, AstraZeneca or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow AstraZeneca monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The trial site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by AstraZeneca, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11 DATA HANDLING AND RECORD KEEPING

11.1 Case Report Forms/Electronic Data Record

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of AstraZeneca and should not be made available in any form to third parties, except for authorized representatives of AstraZeneca or appropriate regulatory authorities, without written permission from AstraZeneca.

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Subject source documents are the physician's subject records maintained at the trial site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, AstraZeneca and the investigator must prospectively document which items will be recorded in the source documents and for which items the CRF will stand as the source document.

11.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or AstraZeneca, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the trial, AstraZeneca should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another investigator, another institution, or to AstraZeneca. The investigator must obtain AstraZeneca's written permission before disposing of any records, even if retention requirements have been met.

12 ETHICS

12.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents, eg, advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to AstraZeneca.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and AstraZeneca in writing within 5 working days after the implementation.

12.2 Ethical Conduct of the Trial

The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

12.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures. In case of data transfer, AstraZeneca will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be agreed to by AstraZeneca and the IRB/IEC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The investigator must ensure that each trial subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any trial-specific activity is performed. The informed consent form used in this trial, and any changes made during the course of the trial, must be prospectively approved by both the IRB/IEC and AstraZeneca before use. The investigator will retain the original of each subject's signed consent form.

13 DEFINITION OF END OF TRIAL

13.1 End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the date of the last post-treatment subject follow-up for tumor assessment and survival.

13.2 End of Trial in all Participating Countries

End of Trial in all participating countries is defined as the date of the last post-treatment subject follow-up for tumor assessment and survival.

14 SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of AstraZeneca. In addition, AstraZeneca retains the right to discontinue development of tremelimumab at any time.

If a trial is prematurely terminated or discontinued, AstraZeneca will promptly notify the investigator. After notification, the investigator must contact all participating subjects within 60 days. As directed by AstraZeneca, all trial materials must be collected and all CRFs completed to the greatest extent possible.

15 PUBLICATION OF TRIAL RESULTS

Publication of trial results is discussed in the Clinical Study Agreement.

16 REFERENCES

1. Ribas A, Camacho LH, Lopez-Berestein G et al. Anti-tumor Activity in Melanoma and Anti-Self Responses in a Phase I trial with the Anti-Cytotoxic T Lymphocyte Associated Antigen 4 Monoclonal Antibody CP-675,206. J Clin Oncol 2005: Vol 23 No 35, Dec 10, 2005

2. Yang, James C. MD, "Tumor regression in patients with metastatic renal cancer treated with a monoclonal antibody to CTLA4 (MDX-010)". Developmental Therapeutics: Immunotherapy (Scientific Program), 2005 ASCO Annual Meeting.

3. Bookman MA, Kloth DD, Korer PE, et.al. Short-course intravenous prophylaxis for paclitaxel-related hypersensitivity reactions. Ann Oncol 1997; 8:611-614.

4. Liberman, P. The use antihistamines in the prevention and treatment of anaphylaxis and anaphylactoid reactions. J Allergy Clin Immunology, 1990; 86 (4II Supp): 684-686.

Appendix 1 List of Abbreviations

AE	adverse event
ANC	absolute neutrophil count
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CRF	case report form
CRP	C reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
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
SGOT	serum glutamic-oxaloacetic transaminase (AST)
SGPT	serum glutamic-pyruvic transaminase (ALT)
T3	triiodothyronine
T4	thyroxine
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell count

Appendix 2 CLINICAL PROTOCOL AMENDMENT 1

Amendment: 1

Amendment No. 1	Date 04 March 2008	Country (ies)	Site(s)

Previous Amendments:

Amendment No.	Date	Country (ies)	Site(s)

SUMMARY

Reason(s) for Amendment

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

- To add hematology to safety laboratory assessments before each dose.
- To clarify that the single safety reference document for CP-675,206 is the product's Investigators Brochure.
- It will not be required that patients enroll within 3 months of completing treatment in their prior protocol.
- To clarify that patients in ongoing trials will not be eligible for this protocol except in extraordinary circumstances.
- To clarify that the Sponsor must approve the enrollment of each patient.
- To clarify that if an investigator wishes to re-treat a patient who has experienced an adverse event that would otherwise require that the patient stop treatment, the investigator must provide the written action plan.
- To add diverticulitis, adverse events requiring infliximab, and immune-mediated thrombocytopenia to the list of adverse events that require that the patient stop treatment.
- To clarify that concomitant medications should not be recorded on the Case Report Form unless they were administered to treat a reportable adverse event.
- To add that patients should be instructed to contact their physician or nurse in case of symptoms which could indicate severe colitis.
- To add instructions for use of infliximab to the diarrhea management algorithm.
- To update the number listed on the vial and carton labels.
- To correct typographical errors.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

The “change from” section represents the current text in the protocol. Bolded text is used to indicate the addition of information to the current text, and strike-out of text (eg, ~~text~~) is used to show the deletion of information from the current text.

The “change to” section represents the revised text, with the revisions shown in the “change from” section in normal text.

Section <Insert section number> , <Insert section title>

Change From

Change To

1. Section SUMMARY, Footnotes for Schedule of Activities, Numbers 3 and 8

Change From

3. Contraception Counseling: All women of childbearing potential must agree to practice a form of effective contraception ~~prior to entry into the study and~~ for 12 months following any dose of study drug.

8. Hematology: WBC with differential count and Absolute Neutrophil Count (ANC), RBC count, Hemoglobin, Hematocrit, Platelet Count

Change To

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.

8. Hematology: WBC with differential count and Absolute Neutrophil Count (ANC), RBC count, Hemoglobin, Hematocrit, Platelet Count.

2. Section 1. INTRODUCTION, 1.2. CP-675,206 Risks and Precautions, Paragraph 7

Change From

The single safety reference document for CP-675,206 is the product's Investigators Brochure and its updates as they become available. Please refer to the Investigators Brochure~~See the current Investigators Brochure for more information on the safety of CP-675,206~~.

Change To

The single safety reference document for CP-675,206 is the product's Investigators Brochure and its updates as they become available. Please refer to the Investigators Brochure.

3. Section 1. INTRODUCTION, 1.3. Rationale for Dosing Hiatus ("Drug Holiday"), Paragraph 2

Change From

One subject who participated in a Phase 1 study of CP-675,206 had a complete response after a single dose of CP-675,206 and has remained free of disease for more than 2 years.[1] ~~All~~ **Most** other subjects who have had objective responses to CP-675,206 have agreed to receive additional doses of the agent, and to date most~~all~~ responses have been durable (>1 year). The value of subsequent doses is not known, but each additional dose has a risk of side effects. In this study, subjects will be allowed to discontinue therapy with the option of receiving additional doses of CP-675,206 at a later time, at the discretion and judgment of the investigator.

Change To

One subject who participated in a Phase 1 study of CP-675,206 had a complete response after a single dose of CP-675,206 and has remained free of disease for more than 2 years.[1] Most other subjects who have had objective responses to CP-675,206 have agreed to receive additional doses of the agent, and to date most responses have been durable (>1 year). The value of subsequent doses is not known, but each additional dose has a risk of side effects. In this study, subjects will be allowed to discontinue therapy with the option of receiving additional doses of CP-675,206 at a later time, at the discretion and judgment of the investigator.

4. Section 4. SUBJECT SELECTION, Paragraph 1

Change From

~~It is expected that subjects will enroll in this protocol within 3 months of completing treatment in their prior protocol. If extenuating circumstances prevent a subject from completing treatment in their prior protocol or from enrolling within this timeframe, the subject may enroll only with written permission by the Sponsor.~~ **It is expected that patients in ongoing trials will not be eligible except in extraordinary circumstances.**

Change To

It is expected that patients in ongoing trials will not be eligible except in extraordinary circumstances.

5. Section 4. SUBJECT SELECTION, 4.3. Randomization Criteria, Paragraph 1, Sentence 1

Addition

The Sponsor must approve the enrollment of each patient.

6. Section 5. TRIAL TREATMENTS, 5.2.1. Formulation and Packaging, Paragraph 3

Change From

The vial and carton labels identify CP-675,206 as "CP-675,206 (clonal), 20 mg/ml IV Vial Solution 400 mg/vial". The study number listed on the vial and carton labels is ~~**"A367CF**~~", "**A367POLS** which is a code for pooled clinical supplies that includes Protocol A3671024.

Change To

The vial and carton labels identify CP-675,206 as "CP-675,206 (clonal), 20 mg/ml IV Vial Solution 400 mg/vial". The study number listed on the vial and carton labels is "A367POLS", which is a code for pooled clinical supplies that includes Protocol A3671024.

7. Section 5. TRIAL TREATMENTS, 5.2.3.3. Stopping Rules for Adverse Events, Paragraph 1 and Bullets 8, 9, and 10

Change From

Subjects who experience any of the following adverse events at any time during the previous cycle must not receive further dosing with CP-675,206 unless the investigator discusses the case with the Pfizer clinician and ~~the Pfizer clinician~~ has provided a written action plan.

- **Diverticulitis**
- **Any adverse event which requires treatment with infliximab**
- **Immune-mediated thrombocytopenia**

Change To

Subjects who experience any of the following adverse events at any time during the previous cycle must not receive further dosing with CP-675,206 unless the investigator discusses the case with the Pfizer clinician and has provided a written action plan.

- Diverticulitis
- Any adverse event which requires treatment with infliximab
- Immune-mediated thrombocytopenia

8. Section 5. TRIAL TREATMENTS, 5.3. Concomitant Medication(s), Paragraph 4

Addition

Concomitant medications should not be recorded on the Case Report Form unless they were administered to treat a reportable adverse event (See Section 8.1).

9. Section 5. TRIAL TREATMENTS, 5.4.1. Management of Diarrhea, Paragraph 1 and Table 5

Change From

Diarrhea is an expected clinically significant adverse event when treating subjects with antiCTLA4 experimental drugs.[2] The diarrhea may be severe, may require hospitalization, and may result in intestinal perforation. **Patients should be instructed to contact their physician or nurse if any of the following occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; inability to get diarrhea under control within 24 hours; or fever or evidence of infection..** The following algorithm (Table 5) is recommended for the treatment of subjects who develop diarrhea while on study.

Table 5. Diarrhea Algorithm

Diarrhea Severity and Duration	Recommendation
Any change indicative of diarrhea	Consider use of probiotics
Grade 1 less than or equal to 14 days	Consider use of probiotics ~~Follow Diarrhea Management Guidelines including~~ *C. difficile* ~~titer~~**toxin**, ~~stool tests~~, oral fluid replacement Consider use of mesalamine and/or empiric loperamide
Grade 1 more than 14 days or Grade 2 of any duration	Consider use of probiotics Evaluation of severity by clinician familiar with CP-675,206-related diarrhea Consider IV fluids if indicated Consider use of budesonide, olsalazine, or mesalmine Consider use of steroids*
Grade 3 or Grade 4 for any duration Or Any grade & duration associated with evidence of severe enterocolitis including bleeding, fever, pain or other signs/symptoms	Consider use of probiotics Evaluation by clinician familiar with CP-675,206-related diarrhea Consider inpatient hospitalization for IV fluids, monitoring Consider use of budesonide, olsalazine, mesalamine, or octreotide Consider use of steroids* **Consider infliximab if patient is unstable or at risk of bowel perforation and not responsive to steroids** Notify the Pfizer Clinician

Change To

Diarrhea is an expected clinically significant adverse event when treating subjects with antiCTLA4 experimental drugs.[2] The diarrhea may be severe, may require hospitalization, and may result in intestinal perforation. Patients should be instructed to contact their physician or nurse if any of the following occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; inability to get diarrhea under control within 24 hours; or fever or evidence of infection.. The following algorithm (Table 5) is recommended for the treatment of subjects who develop diarrhea while on study.

Table 5. Diarrhea Algorithm

Diarrhea Severity and Duration	Recommendation
Any change indicative of diarrhea	Consider use of probiotics
Grade 1 less than or equal to 14 days	Consider use of probiotics *C. difficile* toxin, oral fluid replacement Consider use of mesalamine and/or empiric loperamide
Grade 1 more than 14 days or Grade 2 of any duration	Consider use of probiotics Evaluation of severity by clinician familiar with CP-675,206-related diarrhea Consider IV fluids if indicated Consider use of budesonide, olsalazine, or mesalmine Consider use of steroids*
Grade 3 or Grade 4 for any duration Or Any grade & duration associated with evidence of severe enterocolitis including bleeding, fever, pain or other signs/symptoms	Consider use of probiotics Evaluation by clinician familiar with CP-675,206-related diarrhea Consider inpatient hospitalization for IV fluids, monitoring Consider use of budesonide, olsalazine, mesalamine, or octreotide Consider use of steroids* Consider infliximab if patient is unstable or at risk of bowel perforation and not responsive to steroids Notify the Pfizer Clinician

10. Section 7. ASSESSMENTS, 7.3. Laboratories, Paragraph 1

Change From

Laboratory assessments will 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, TSH.**, hematology tests including WBC with differential count and Absolute Neutrophil Count (ANC), RBC count, Hemoglobin, Hematocrit, and Platelet Count.** Investigators should ~~use~~ **review** the results of ~~the~~ **all** laboratory tests **and use them** to make re-dosing decisions.

Change To

Laboratory assessments will 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, TSH., hematology tests including WBC with differential count and Absolute Neutrophil Count (ANC), RBC count, Hemoglobin, Hematocrit, and Platelet Count. Investigators should review the results of all laboratory tests and use them to make re-dosing decisions.

11. Section Appendix 1. List of Abbreviations

Addition

ANC **absolute neutrophil count**

Appendix 3 CLINICAL PROTOCOL AMENDMENT 2

Current Amendment: 2

Amendment No. 2	Date 26 December 2019	Country (ies)	Site(s)

Previous Amendments:

Amendment No. 1	Date 04 March 2008	Country (ies)	Site(s)

SUMMARY

Reason(s) for Amendment

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

- To implement the administrative change in 2012 including changes in sponsor, compound name, study number, and specific manual name.
- To update safety information of tremelimumab according to changes in Investigator's Brochures of tremelimumab released since last protocol amendment.
- To update that each carton will contain 4 vials of tremelimumab instead of 16.
- To introduce the Safety Management Guidelines (TMG) and to inform that TMG will be delivered as a standalone Annex document.
- To provide clarifications of the time database lock and final analysis
- To add language on options patients have after database lock and final analysis.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

The "change from" section represents the current text in the protocol. Colored and underlined text (e.g., text) is used to indicate the addition of information to the current text, and colored and strike-out of text (eg, ~~text~~) is used to show the deletion of information from the current text.

The "change to" section represents the revised text, with the revisions shown in the "change from" section in normal text.

Section <Insert section number> , <Insert section title>

Change From

Change To

1. Entire Protocol

Change from

~~CP-675,206~~tremelimumab

Change to

Tremelimumab

Change from

~~Pfizer~~AstraZeneca

Change to

AstraZeneca

Change from

~~A3671024~~D4881C00024

Change to

D4881C00024

Change from

~~Dosage and Administration Instructions~~ Investigational Product Manual

Change to

Investigational Product Manual

2. Section SUMMARY, "Trial Design"

Change from

This is a multi-center, international, open label study. Eligible subjects are those who have received ~~CP-675,206~~tremelimumab in another protocol but are no longer going to receive ~~CP-675,206~~tremelimumab in the other trial. All subjects who are enrolled in this trial will have the opportunity to receive ~~CP-675,206~~tremelimumab. Doses may be delayed ~~or suspended indefinitely ("dosing hiatus")~~under certain circumstances at the discretion of the investigator~~, and the subject may remain in the study.~~. Subjects not receiving ~~CP-675,206~~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.

Change to

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

3. Section SUMMARY, "Trial Treatment", Fourth paragraph

Change from

Doses may be delayed ~~or suspended indefinitely ("dosing hiatus")~~under certain circumstances at the discretion of the investigator~~,~~:

- Dosing may be delayed per the Dosing Modification and ~~the subject may remain in the study.~~ Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.

Subjects not receiving ~~CP-675,206~~tremelimumab should be seen in the clinic or contacted at least every 6 months to determine their tumor status~~.~~ until the time of the final analysis.

Change to

Doses may be delayed under certain circumstances at the discretion of the investigator:

- Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.

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 the final analysis.

4. Section 1.2 "Tremelimumab Risks and Precautions"

Replace the entire section with

Risks with tremelimumab monotherapy include, but are not limited to, gastrointestinal effects (colitis, diarrhea, enterocolitis, intestinal perforation, and large intestinal perforation); endocrine disorders (hypo- and hyperthyroidism, hypophysitis, and adrenal insufficiency); skin effects (rash and pruritus); lipase and/or amylase elevations and clinical manifestations of pancreatitis; hepatic events (including immune-mediated hepatitis and liver enzyme

elevations); pneumonitis and ILD; neurotoxicity (including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barré syndrome); thrombocytopenia, anemia, and neutropenia; infusion-related reactions and hypersensitivity/anaphylactic reactions; renal events (including nephritis/autoimmune nephritis and acute kidney injury); autoimmune arthritis, Sjogren's syndrome; giant cell temporal arteritis, and ulcerative colitis; and hyperglycemia and diabetes mellitus.

For information on all identified and potential risks for tremelimumab, please always refer to the current version of the tremelimumab IB.

In monotherapy clinical studies, AEs reported at an incidence of ≥ 20% include events such as diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, and vomiting. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab, and approximately 45% of patients experienced an SAE. Please see the current version of the tremelimumab IB for a detailed summary of tremelimumab monotherapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the tremelimumab program.

5. Section 1.3, Rational for Dosing Hiatus ("Drug Holiday")

Remove the entire section

6. Section 5 "TRIAL TREATMENT", Fourth paragraph

Change from

Doses may be delayed ~~or suspended indefinitely ("dosing hiatus")~~under certain circumstances at the discretion of the investigator~~,~~:

- Dosing may be delayed per the Dosing Modification and ~~the subject may remain in the study.~~ Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.

Subjects not receiving ~~CP-675,206~~tremelimumab should be seen in the clinic or contacted at least every 6 months to determine their tumor status~~.~~ until the time of the final analysis.

Change to

Doses may be delayed under certain circumstances at the discretion of the investigator:

- Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.

- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.

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 the final analysis.

7. Section 5.2.1 "Formulation and Packaging", Third and fourth paragraph

Change from

The vial and carton labels identify ~~CP-675,206~~tremelimumab as "~~CP-675,206~~tremelimumab (clonal), 20 mg/ml IV ~~Vial Solution~~VialSolution 400 mg/vial". The ~~study number listed on the vial and carton labels is "A367POLS", which is a code for pooled clinical supplies that includes Protocol A3671024.~~
~~During the course of this trial the formulation, packaging, and/or labeling of CP-675,206 may change. The latest~~lastest formulation, packaging and labeling will be provided in an updated ~~Dosage and Administration Instructions document.~~ Investigational Product Manual. Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

Change to

The vial and carton labels identify tremelimumab as "tremelimumab (clonal), 20 mg/ml IV VialSolution 400 mg/vial". The lastest formulation, packaging and labeling will be provided in an updated Investigational Product Manual. Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

8. Section 5.2.3.1 "Dose Reduction of CP-675,206"

Move the section to Section 5.4 "Management of Toxicity and Dose Modification Information of Tremelimuab"

9. Section 5.2.3.2 "Dose Delays and Re-Dosing Criteria for of CP-675,206"

Change from

5.2.3.1 ~~5.2.3.2.~~ Dose Delays and Re-Dosing Criteria for ~~CP-675,206~~Tremelimumab

The initiation of a cycle may be delayed to allow ~~-~~recovery from treatment-related toxicity. ~~All subjects must meet the following criteria for laboratory parameters by the day of dosing, as detailed in Table 2, in order to be treated with CP-675,206.~~

~~**Table 2. Re-Dosing Criteria for CP-675,206: Laboratory Parameters**~~

Laboratory Parameter	Re-Dosing Criteria
Hepatic Function (within 10 days)	• AST, ALT ≤2.5 x ULN (≤5 x ULN if liver metastases are present) bilirubin ≤2 x ULN (except in subject with Gilbert's syndrome)
Amylase and Lipase (within 10 days)	• ≤1.5 x ULN or baseline

For all subjects, treatment-related adverse events must have resolved at least to CTCAE Grade 1 or baseline (at the start of this study) and be considered tolerable by the day of dosing, in order to be treated with CP-675,206, except as noted in Table 3 and in Section 5.2.3.3 (Stopping Rules for Adverse Events).

Table 3. Re-Dosing Criteria for CP-675,206: Treatment-Related Adverse Events.

Adverse Event	Re-Dosing Criteria
Thyroiditis	Asymptomatic or stable on thyroid replacement therapy
Rash	Tolerable and ≤ Grade 2
Vitiligo	May be re-dosed regardless of severity
All other treatment-related adverse events	Tolerable and ≤ Grade 1 or baseline

NOTE: If a subject has a hypersensitivity reaction to CP-675,206 or a Grade 3 treatment-related toxicity at any time during a cycle, the investigator must notify the Pfizer Clinician.

There is a concern that subjects with active brain metastases may be at risk for increased intracranial pressure if treated with CP-675,206. tremelimumab. Subjects with brain metastases must not receive CP-675,206tremelimumab until after the metastases have been adequately treated with surgery and/or radiation.

Subjects must not receive CP-675,206tremelimumab while pregnant or breast-feeding. Females of childbearing potential must have a negative serum or urine pregnancy test within 10 days prior to each dose. -Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential.

For details on dosing delays and re-dosing criteria, please refer to the Dosing Modification and Toxicity Management Guidelines, which is delivered as an Annex document.

Change to

5.2.3.1 Dose Delays and Re-Dosing Criteria for Tremelimumab

The initiation of a cycle may be delayed to allow recovery from treatment-related toxicity.

There is a concern that subjects with active brain metastases may be at risk for increased intracranial pressure if treated with tremelimumab. Subjects with brain metastases must not

receive tremelimumab until after the metastases have been adequately treated with surgery and/or radiation.

Subjects must not receive tremelimumab while pregnant or breast-feeding. Females of childbearing potential must have a negative serum or urine pregnancy test within 10 days prior to each dose. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential.

For details on dosing delays and re-dosing criteria, please refer to the Dosing Modification and Toxicity Management Guidelines, which is delivered as an Annex document.

10. Section 5.2.3.3 "Stopping Rules for Adverse Events"

Change from

5.2.3.2~~5.2.3.3~~ Stopping Rules for Adverse Events

Subjects who experience any of the following adverse events at any time during the previous cycle must not receive further dosing with ~~CP-675,206~~tremelimumab unless the investigator discusses the case with the ~~Pfizer clinician~~AstraZeneca study physician and has provided a written action plan.

- ~~Any Grade 4 CP-675,206-related adverse event~~
- Hypersensitivity to ~~CP-675,206~~tremelimumab, Grade 3 (see Section 5.4.~~2~~1)
- Hypersensitivity to ~~CP-675,206~~tremelimumab, Grade 2, and symptoms reappear after infusion restarted
- Melanoma associated retinopathy, Grade 2 or above
- Uveitis, Grade 2 or above
- ~~Hepatitis, Grade 3~~
- ~~Diarrhea, Grade 3, requiring treatment with systemic steroids for more than 10 days in any 3-month period~~
- Diverticulitis
- ~~Any adverse event which requires treatment with infliximab~~
- Immune-mediated thrombocytopenia

Change to

5.2.3.2 Stopping Rules for Adverse Events

Subjects who experience any of the following adverse events at any time during the previous cycle must not receive further dosing with tremelimumab unless the investigator discusses the case with the AstraZeneca study physician and has provided a written action plan

- Hypersensitivity to tremelimumab, Grade 3 (see Section 5.4.1)
- Hypersensitivity to tremelimumab, Grade 2, and symptoms reappear after infusion restarted
- Melanoma associated retinopathy, Grade 2 or above
- Uveitis, Grade 2 or above
- Diverticulitis
- Immune-mediated thrombocytopenia

11. Section 5.2.6 "Treatment after the End of the Study"

Add

After the final analysis, AstraZeneca will continue to supply open-label drug to patients receiving tremelimumab therapy up to the time that they discontinue the treatment for whatever reason (see Section 6.3). At the time of the final analysis and thereafter:

- Assessment will revert to standard of care at particular site
- There would be no more data collection except for SAE reporting. Clinical study database would be closed
- Paper form process would be used for SAE reporting. All SAEs, overdoses and pregnancies would be reported until 90 days after last dose
- Drug dispensation and reconciliation will be handled by site on each patient's visit

Study would be opened until last patient treated. Final last subject last visit will be defined as last patient's treatment discontinuation

12. Section 5.3 "Concomitant Medication (s)", Table 4

Change from

Protocol #	Indication	Allowed Anti-Cancer Therapy
A3671006	Breast Cancer	exemestane (Aromasin)
~~A3671025~~	~~Renal Cell Carcinoma~~	~~sunitinib malate (Sutent)~~

Patients from Renal Cell Carcinoma studies should not receive sunitinib within 3 months of a dose of tremelimumab, as acute renal failure has been reported with combination therapy of tremelimumab and sunitinib. It is unknown whether there could be a safety issue with combination of tremelimumab and other tyrosine kinase inhibitors.

Change to

Protocol #	Indication	Allowed Anti-Cancer Therapy
A3671006	Breast Cancer	exemestane (Aromasin)

Patients from Renal Cell Carcinoma studies should not receive sunitinib within 3 months of a dose of tremelimumab, as acute renal failure has been reported with combination therapy of tremelimumab and sunitinib. It is unknown whether there could be a safety issue with combination of tremelimumab and other tyrosine kinase inhibitors.

13. Section 5.4 "Management of Toxicity of CP-675,206"

Change the Section Title from

5.4 Management of Toxicity and Dose Modification Information of ~~CP-675,206~~Tremelimumab

Change to

5.4 Management of Toxicity and Dose Modification Information of CP-675,206Tremelimumab

14. Section 5.4 "Management of Toxicity and Dose Modification Information of CP-675,206Tremelimumab "

Replace the introductory text of the Section 5.4 and entire Section 5.4.1 "Management of Diarrhea" with

Comprehensive toxicity management guidelines (TMG) have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitors durvalumab [Medi4736] (PD-L1 inhibitor) and tremelimumab (CTLA4 inhibitor). Given the similar underlying mechanisms of toxicities observed with these two compounds, these guidelines are applicable to the management of patients receiving either drug as monotherapy or in combination. Additionally, these guidelines are applicable when either drug is used alone or in combination and is administered concurrently or sequentially with other anti-cancer drugs (i.e. antineoplastic chemotherapy, targeted agents), as part of a protocol specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications

(including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment. The most current version of the TMGs entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy" is provided to the investigative site as an Annex document and is maintained within the Site Master File.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related. In addition, there are certain circumstances in which tremelimumab should be permanently discontinued (see Section 5.2.3.2. of this protocol and the Dosing Modification and Toxicity Management Guidelines). Following the first dose of IP, subsequent administration of tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to tremelimumab monotherapy regimen by the reporting Investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

15. Section 5.4 "Mangement of Toxicity of CP-675,206"

Add

Section 5.4.2 "Medication Errors"

The definition of a Medication Error can be found in Appendix 4.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, i.e., immediately but no later than 24 hours after he/she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.2) and within 30 days for all other medication errors.

16. Section 6.3 "End of Treatment"

Add

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.

15. Section 8.2.1 "Immediate Reporting of Serious Adverse Events"

Change from

Serious adverse events require immediate notification to ~~Pfizer~~AstraZeneca or its designated representative beginning from the time that the subject provides informed consent for the study; and should be reported under the patient's prior protocol until the patient receives investigational product in this study. SAEs do not require notification if ~~the patient~~it has been ~~placed on drug holiday,~~ at least 90 days ~~have passed~~ since the previous dose of ~~CP-675,206~~tremelimumab, and at least 28 days ~~have passed~~ since any study-related procedures for the patient.

Change to

Serious adverse events require immediate notification to AstraZeneca or its designated representative beginning from the time that the subject provides informed consent for the study; and should be reported under the patient's prior protocol until the patient receives investigational product in this study. SAEs do not require notification if it has been at least 90 days since the previous dose of tremelimumab, and at least 28 days since any study-related procedures for the patient.

16. Section 8.2.2 "Reporting of Adverse Events in Case Report Forms"

Change from

Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of trial treatment. ~~Collection of new adverse events should be discontinued after 90 days post-dose during a drug holiday with the exception that SAEs with a suspected causal relationship to CP-675,206 are still reportable.~~

Change to

Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of trial treatment.

17. APPENDIX 4 "Medication Error"

Added "Appendix 4 Medication Error"

Appendix 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.